The results of these recent U.S. and Canadian cohort studies demonstrate a consistent, positive association between long-term $PM_{2.5}$ exposure and mortality across various spatial extents, exposure assessment metrics, statistical techniques, and locations, including those where mean annual average concentrations are below ≤12 μg/m^3. Recent cohort studies in the U.S. observed increases in total mortality and mortality due to cardiovascular disease in separate cohorts of men and women. Additional cohort studies conducted in Europe observed similarly consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality (see Table 11-6), and support the evidence from the U.S. and Canada. Particularly noteworthy is a study conducted in Europe that combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and total (nonaccidental) (Beelen et al., 2014a), cardiovascular (Beelen et al., 2014b), and respiratory (Dimakopoulou et al., 2014) mortality. Including participants from 13 European countries, the authors applied a common statistical protocol to data from each of the 22 cohorts in the first stage of the analysis and combined the cohort-specific effects in a second stage. The authors observed a positive association between long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality (HR: 1.07, 95% CI 1.02, 1.13) (Beelen et al., 2014a), but the associations for cardiovascular and respiratory mortality were near the null value, except for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.21, 95% CI: 0.87, 1.69) (Beelen et al., 2014b).

Table 11-6 European epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean SD in μg/m^3	Copollutant Examination
†Beelen et al. (2014a) Multicity; Europe $PM_{2.5}$: 2008–2011 Follow-up: 1985–2007 (variable, depending on cohort) Pooled Cohort Study	ESCAPE: 367,251 participants; 5,118,039 person-years of follow-up; 29,076 deaths	LUR; model validation R^2 = 0.57–0.89	Mean: 6.6–31.0	Correlation (*r*): $PM_{10-2.5}$: 0.11–0.90 NO_2: 0.17–0.88 Copollutant models with: copollutant models limited to cohorts for which pollutant correlation was <0.7
†Beelen et al. (2014b) Multicity; Europe $PM_{2.5}$: 2008–2011 Follow-up: 1985–2007 (variable, depending on cohort) Pooled Cohort Study	ESCAPE: 22 cohorts from 13 European countries 367,383 participants; 5,119,317 person-years of follow-up; 9,994 deaths due to CVD	LUR; model validation R^2 = 0.57–0.89	Mean: 6.6–31.0	Correlation (*r*): NA Copollutant models with: NA
†Beelen et al. (2009) Multicity; Netherlands $PM_{2.5}$: 1987–1996 Follow-up: 1987–1996	NLCS: 1,117,528 participants; 6,137 CVD deaths	Interpolation of measurements from national fixed-site monitoring network	NA	Correlation (*r*): NA Copollutant models with: NA

Table 11-6 (Continued): European epidemiologic studies of long term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean SD in µg/m³	Copollutant Examination
†Bentayeb et al. (2015) Multicity, France $PM_{2.5}$: 1989–2008 Follow-up: 1989–2013 Cohort Study	Gazel cohort: 20,327 participants 1,967 deaths	CHIMERE chemical transport model (2 km resolution)	Mean: 15.0	Correlation (*r*): NA Copollutant models with Copollutant models conducted with correlation between pollutants was <0.7 (O_3, benzene).
†Carey et al. (2013) Multicity; England $PM_{2.5}$: 2002 Follow-up: 2003–2007 Cohort Study	National English Cohort: 835,607 patients ages 40–89; 83,103 deaths	Dispersion model, 1 km grid cells; model validation R^2 = 0.23–0.71	Mean: 12.9	Correlation (*r*): PM_{10}: 0.99 SO_2: 0.46 NO_2: 0.85 O_3: −0.39 Copollutant models with: SO_2, O_3
†de Keijzer et al. (2016) Multicity; Spain $PM_{2.5}$: 2009–2013 Follow-up: 2009–2013 Ecologic Study	Mortality data from 2,148 small areas covering Spain	CALIOPE Air Quality Forecasting System (combines meteorological, emissions, chemical transport and atmospheric mineral dust models)	Mean: 8.22	Correlation (*r*): PM_{10}: 0.91 NO_2: 0.55 O_3: 0.33 Copollutant models with: NA
†Dehbi et al. (2016) Multicity: UK $PM_{2.5}$: 2010–2011 Follow-up: 1989–2015 Pooled Cohort Study	Combines data from two British cohorts: Medical Research Council National Survey of Health and Development (4,400 participants born in March 1946) and Southall and Brent Revisited study (3,129 tri-ethnic men and women recruited 1989–1991)	Exposure data same as used in ESCAPE Cohort; see Beelen et al. (2014a)	Median: 9.90	Correlation (*r*): NO_2: 0.83 NO_X: 0.82 PM_{10}: 0.60 $PM_{10-2.5}$: 0.35 Copollutant models with: NA
†Dimakopoulou et al. (2014) Multicity; Europe $PM_{2.5}$: 2008–2011 Follow-up: 1985–2007 (variable, depending on cohort) Pooled Cohort Study	ESCAPE: 16 cohorts from 11 European countries 307,553 participants; 1,559 deaths due to nonmalignant respiratory disease	LUR; model validation R^2 = 0.57–0.89	Mean: 7.1–31.0	Correlation (*r*): NA Copollutant models with: NA
Naess et al. (2007) Oslo, Norway $PM_{2.5}$: 1992–1995 Follow-up: 1992–1998 Cohort Study	Oslo Cohort: 143,842 individuals ages 51–90	AirQUIS dispersion model; model validation (*r* = 0.57 [summer)], –0.79 [winter]) reported in Oftedal et al. (2009)	Mean: 15	Correlation (*r*): NO_2: *r* > 0.88 PM_{10}: *r* > 0.88 Copollutant models with: NA

Table 11-6 (Continued): European epidemiologic studies of long term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean SD in µg/m³	Copollutant Examination
†Tonne et al. (2015) London; U.K. $PM_{2.5}$: 2003–2010 Follow-up: 2003–2010 Cohort Study	MINAP: 18,138 participants with hospital admissions between 2003–2007; 5,129 deaths	KCLurban dispersion model; see Beevers et al. (2013) for details	Mean: 14.6	Correlation (*r*): NO_2: 0.71 NO_X: 0.73 O_3: −0.82 PM_{10}: 0.96 $PM_{10-2.5}$: 0.70 Copollutant models with: NA

NR = not available; km = kilometer; LUR = land use regression; CVD = cardiovascular disease; ESCAPE = European Study of Cohorts for Air Pollution Effects; NLCS = Netherlands Cohort Study on Diet and Cancer; MINAP = Myocardial Ischaemia National Audit Project.

†Studies published since the 2009 PM ISA.

11.2.2.3 Cardiovascular Mortality

Overall, the results of the recent U.S. and Canadian cohort studies demonstrate a consistent, positive association between long-term $PM_{2.5}$ exposure and cardiovascular mortality across various spatial extents, exposure assessment techniques, and statistical techniques, and locations, including those where mean annual average concentrations are ≤12 µg/m³. Additional cohort studies conducted in Europe observed similarly consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (see Table 11-6), and support the evidence from the U.S. and Canada. However, a study conducted in Europe that combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and cardiovascular mortality (Beelen et al., 2014b) reported associations near the null value, except for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.21, 95% CI: 0.87, 1.69). More detailed results of long-term $PM_{2.5}$ exposure and cardiovascular mortality are included in Section 6.3.9.

11.2.2.4 Respiratory Mortality

Overall, the results of these recent U.S. cohort studies demonstrate a generally consistent, positive association between long-term $PM_{2.5}$ exposure and respiratory mortality, though the results from the two Canadian studies are inconsistent. In addition, a study conducted in Europe that pooled data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and respiratory mortality observed an association for respiratory mortality near the null value (Dimakopoulou et al., 2014). Overall, the associations for respiratory mortality were generally positive, though some inconsistencies among the results from different analyses of the same cohort provide some uncertainty in the stability of these results [Ostro et al. (2010) and Ostro et al. (2015); Crouse et al. (2015) and Pinault et al. (2016)]. Recent studies have evaluated the association between long-term $PM_{2.5}$ exposure and COPD mortality, a cause of death for which there has previously been little examination. These studies report

modest positive associations with COPD mortality and the hazard ratios are generally less precise (i.e., wider 95% confidence intervals) than those for respiratory mortality. More detailed results of long-term $PM_{2.5}$ exposure and cardiovascular mortality are included in Section 5.2.10.

11.2.2.5 Causal Inference Studies

Recently, several studies have explored the use of causal inference methods (i.e., quantitative methods and/or study design attributes) to specifically inform the causal nature of the relationship between long-term $PM_{2.5}$ exposure and mortality. A recent study employed a difference-in-difference approach as a quantitative causal inference method to examine the relationship between long-term $PM_{2.5}$ exposure and mortality in New Jersey (Wang et al., 2016). $PM_{2.5}$ concentrations were estimated at the census tract level using similar exposure assessment techniques as those used by Shi et al. (2015), discussed previously. The difference-in-difference method controls for geographical differences using dummy variables for each tract, long-term temporal trends using dummy variables for each year, and temperature, which is both correlated with $PM_{2.5}$ and can vary differentially over space and time. Wang et al. (2016) observed a positive relationship between long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality (RR: 1.08; 95% CI: 1.01, 1.15). Cox and Popken (2015) conducted an ecologic, county-level, repeated-measures analysis to evaluate the changes in $PM_{2.5}$ concentrations from 2000 to 2010 in 15 large U.S. states, and the association with age-specific mortality rates for older adults (65+ years) over the same period. The authors observed positive correlations between county-level $PM_{2.5}$ concentrations and county-level mortality rates for total (nonaccidental) and cardiovascular mortality, but not for external-cause mortality (e.g., accidents), a negative control. The authors applied several quantitative methods to inform causal inference (e.g., Granger tests), and observed effects in 6–7% of counties studied (Cox and Popken, 2015). Inference from this study is limited by a lack of individual-level data; it is an ecologic study relying on county-level mortality rates, with no control for potential confounders other than age, making it difficult to adequately interpret the results. Overall, the results of these causal inference studies contribute to the body of epidemiologic evidence that informs the causal relationship between long-term $PM_{2.5}$ exposure and total mortality. Observing consistent results for this relationship across studies using different analytic techniques (i.e., difference-in-difference approach) increases our confidence in the relationship.

11.2.2.6 Studies of Temporal Trends and Life Expectancy

A recent series of studies has added to the body of evidence on the relationship between long-term exposure to $PM_{2.5}$ and mortality by examining the temporal trends in $PM_{2.5}$ concentrations and changes in life expectancy, testing the hypothesis that decreases in $PM_{2.5}$ concentrations would be associated with increases in life expectancy. Pope et al. (2009) used air quality data in a cross-sectional analysis from 51 metropolitan areas across the U.S., beginning in the 1970s through the early 2000s, to

demonstrate that a 10 μg/m^3 decrease in long-term $PM_{2.5}$ concentration was associated with a 0.61-year increase in life expectancy. In a subsequent analysis, these authors extended the period of analysis to include 2000 to 2007 (Correia et al., 2013). While the decline in concentrations of $PM_{2.5}$ was slower for the 2000 to 2007 period, compared to the period from 1980 to 2000, a decrease in long-term $PM_{2.5}$ concentration continued to be associated with an increase in life expectancy, though the magnitude of the increase was smaller than in the previous analysis and the earlier time period (10 μg/m^3 decrease in long-term $PM_{2.5}$ concentration was associated with a 0.35-year increase in life expectancy). It is noteworthy that, by 2007, 48 of the 545 counties included in the study were not in compliance with the NAAQS (at that time, the annual standard was 15 μg/m^3). The mean concentration across all counties was 13.2 μg/m^3 in 2000, and decreased to 11.6 μg/m^3 by 2007. Using a doubly robust additive hazards model, Wang et al. (2017a) calculated that a 1 μg/m^3 decrease in the annual concentration of $PM_{2.5}$ would prevent about 5,400 premature deaths among the 13.1 million Medicare beneficiaries in seven southeastern states analyzed in Wang et al. (2017b). In an analysis conducted in Spain, de Keijzer et al. (2016) focused on the years of life lost associated with an increase in $PM_{2.5}$ rather than the life expectancy gain associated with a decrease in $PM_{2.5}$. They observed 0.64 (95% CI 0.59, 0.70) years of life lost for every 2 μg/m^3 increase in $PM_{2.5}$. Evaluating life expectancy in a different manner, Baccarelli et al. (2016) conducted an ecologic study to investigate whether or not there was an association between county-level $PM_{2.5}$ concentrations and the proportion of 55−64 and 70- to 74-year-olds that survived for an additional 30 years. They started with the numbers of 55−64 and 70- to 74-year-olds in 3,034 U.S. counties in 1980 and compared it with the numbers of 85−94 and 100- to 104-year-olds in 2010 in each county, using county-level $PM_{2.5}$ estimated from a hybrid of LUR and BME and averaged from 1999−2008. They observed that counties with higher estimated $PM_{2.5}$ concentrations were associated with a lower proportion of adults reaching age 85 years or more.

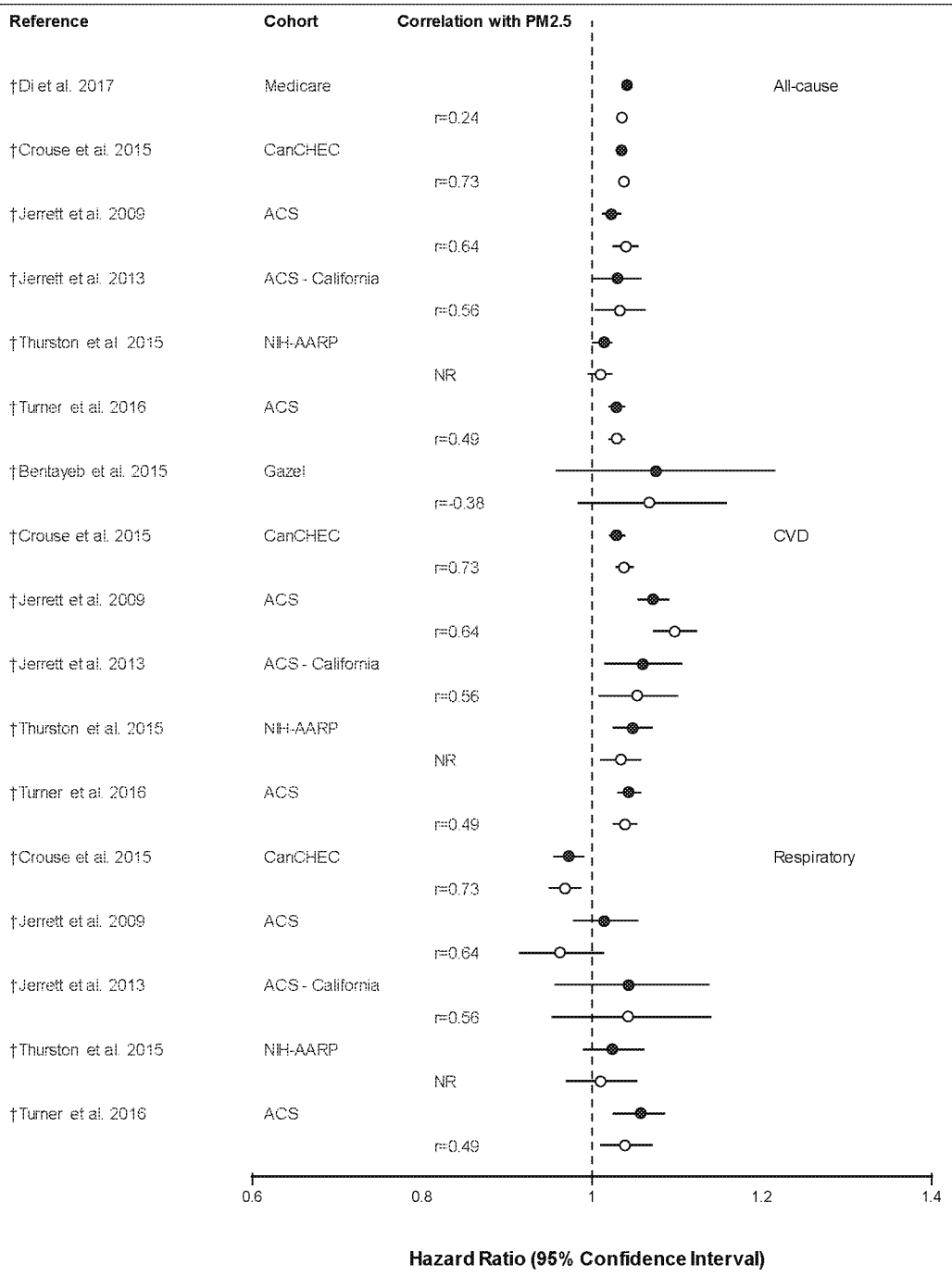
11.2.3 Potential Copollutant Confounding of the $PM_{2.5}$-Mortality Relationship

In the examination of potential confounding effects of copollutants on the relationship between long-term $PM_{2.5}$ exposure and mortality, it is informative to evaluate whether $PM_{2.5}$ risk estimates are changed in copollutant models. Recent studies have examined the potential for copollutant confounding by evaluating copollutant models that include O_3 (Figure 11-20), NO_2, $PM_{10-2.5}$, SO_2, and benzene (Figure 11-21). These recent studies address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of co-exposure to correlated copollutants in long-term analyses.

The results for associations between long-term $PM_{2.5}$ exposure and mortality in single pollutant models and copollutant models adjusted for O_3 are shown in Figure 11-20. The correlations between $PM_{2.5}$ and O_3 exposures in the studies that conducted copollutant analyses were generally positive and moderate to strong, ranging from r = 0.49 to 0.73, except for two studies which reported a weak-to-

moderate negative correlation [$r = -0.38$; (Bentayeb et al., 2015) and $r = -0.24$; (Di et al., 2017c)]. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for O_3. The trend persisted for total (nonaccidental) mortality, as well as mortality due to cardiovascular or respiratory disease. There were several exceptions to the trend. The effect of long-term $PM_{2.5}$ exposure on CHD mortality among women in the AHSMOG cohort (Chen et al., 2005) increased after adjusting for O_3 in the model. Conversely, the effect of long-term $PM_{2.5}$ exposure on respiratory mortality in the ACS cohort (Jerrett et al., 2009) decreased (and changed from positive to negative) after adjusting for O_3 in the model.

The results for associations between long-term $PM_{2.5}$ exposure and mortality in single pollutant models and copollutant models adjusted for NO_2, $PM_{10-2.5}$, SO_2, or benzene are shown in Figure 11-21. The correlations between $PM_{2.5}$ and NO_2 exposures in studies that conducted copollutant analyses were positive and weak ($r = 0.25$) or moderate ($r = 0.40$; $r = 0.55$). The correlations between $PM_{2.5}$ and $PM_{10-2.5}$ were not reported in one study (Puett et al., 2009), and in another meta-analysis, the copollutant analyses were limited to cohorts that reported a correlation of $r < 0.7$. One study evaluated SO_2 (Chen et al., 2005) and another benzene (Bentayeb et al., 2015) in copollutant models, and reported correlations of $r = 0.30$ and $r = 0.66$, respectively. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for NO_2, $PM_{10-2.5}$, SO_2, or benzene.

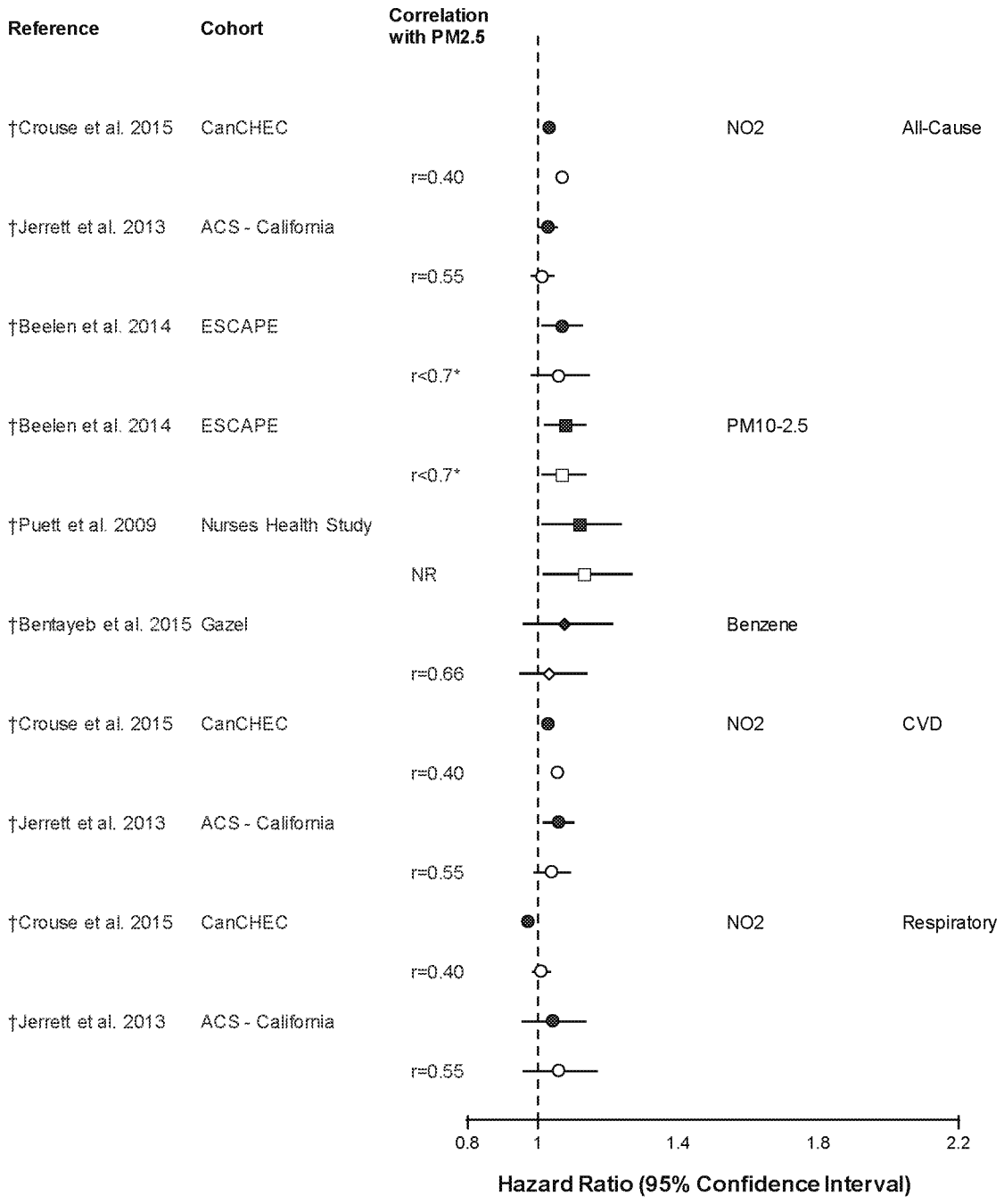


ACS = American Cancer Society Cohort; CanCHEC = Canadian Census Health and Environment Cohort; CVD = cardiovascular disease; NIH-AARP = National Institutes of Health American Association of Retired Persons Diet & Health Cohort; NR = not reported.

Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Closed circles represent effect of $PM_{2.5}$ in single pollutant models, open circles represent effect of $PM_{2.5}$ adjusted for O_3.

Corresponding quantitative results reported in Supplemental Table S11-7 (U.S. EPA, 2018b).

Figure 11-20 Associations between long-term exposure to $PM_{2.5}$ and mortality in single pollutant models and models adjusted for O_3.



Note: †Studies published since the 2009 PM ISA. Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles, squares, triangles and diamonds represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled symbols represent effect of $PM_{2.5}$ in single pollutant models, open circles represent effect of $PM_{2.5}$ adjusted for NO_2; open squares represent effect of $PM_{2.5}$ adjusted for $PM_{10-2.5}$; open triangles represent effect of $PM_{2.5}$ adjusted for SO_2; open diamonds represent effect of $PM_{2.5}$ adjusted for benzene. *includes cohorts from meta-analysis where the correlation was less than 0.7.

ACS = American Cancer Society Cohort; CanCHEC = Canadian Census Health and Environment Cohort; CVD = cardiovascular disease; NR = not reported.

Corresponding quantitative results reported in Supplemental Table S11-8 (U.S. EPA, 2018b).

Figure 11-21 Long-term exposure to $PM_{2.5}$ and mortality in single pollutant models and models adjusted for other pollutants.

11.2.4 Evaluation of the $PM_{2.5}$-Mortality Concentration-Response Relationship

An important consideration in characterizing the association between long-term $PM_{2.5}$ exposure and mortality is whether the concentration-response relationship is linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. The 2009 PM ISA characterized the results of an analysis by Schwartz et al. (2008) that demonstrated that the shape of the concentration-response curve was generally linear.

A number of recent studies have conducted analyses to inform the shape of the concentration-response relationship for the association between long-term exposure to $PM_{2.5}$ and mortality, and are summarized in Table 11-7. Generally, the results of these analyses continue to support a linear, no-threshold relationship for total (nonaccidental) mortality, especially at lower ambient concentrations of $PM_{2.5}$ (i.e., $\leq$12 $\mu g/m^3$). Lepeule et al. (2012), Di et al. (2017c) and Shi et al. (2015) observed linear, no-threshold concentration-response relationships for total (nonaccidental) mortality, with confidence in the relationship down to a concentration of 8, 5, and 6 $\mu g/m^3$, respectively (Figure 11-22). Similar linear, no-threshold concentration-response curves were observed for total (nonaccidental) mortality in other studies (Chen et al., 2016; Hart et al., 2015; Thurston et al., 2015; Cesaroni et al., 2013). Pinault et al. (2016) demonstrated that though the relationship was not statistically different than linear across the range of $PM_{2.5}$ concentrations observed in the study, the slope of the line tended to be steeper at lower concentrations (Figure 11-23), and Crouse et al. (2015) reported a supralinear model was a better fit to the data than the linear model (Figure 11-23). In contrast, Villeneuve et al. (2015) observed that the best fit for the long-term $PM_{2.5}$ exposure—total (nonaccidental) mortality relationship was in a threshold model with a threshold at 11 $\mu g/m^3$ (Figure 11-23). In addition, there is emerging evidence for a nonlinear concentration-response function for some causes of death (Section 6.3.9.2).

Table 11-7 Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality.

Study Location—Cohort Table/Figure from Reference	Exposure $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
†Beelen et al. (2014a) Europe–ESCAPE (Table 5; Figure on appendix pg. 51)	LUR NR; (6.6–31.0)	Cut-point Analysis—include only participants with exposure estimates below prespecified thresholds (25, 20, 15, 10 $\mu g/m^3$). Studied shape of association for each cohort by inputting exposure term as natural cubic spline. HRs remained positive and statistically significant when only participants with exposure concentrations below 25 and 20 $\mu g/m^3$ were included. Below 15 $\mu g/m^3$, HRs were elevated but less precise (i.e., wider 95% confidence intervals). Results of spline model show no deviation from linear relationship.
†Cesaroni et al. (2013) Italy–RoLS (Figure 2B)	Eulerian Dispersion Model (1 × 1 km) 23.0; (7.2–32.1)	Natural splines with 2, 3, or 4 df; compared goodness of fit using BIC and likelihood ratio test No evidence of deviation from linearity. Results similar for 2, 3 or 4 degrees of freedom
†Chen et al. (2016) Canada–EFFECT (Figure 2)	Satellite-based methods (10 × 10 km) 10.7; (1.2-18.0)	Natural splines with 2, 3, or 4 df, compared goodness of fit using AIC. Comparisons made with 2.2 $\mu g/m^3$ No evidence for departure from linearity
†Crouse et al. (2012) Canada–CanCHEC (Figure 2A-D)	Fixed-site monitors in 11 cities; Satellite-based methods (10 × 10 km) 11.2; (1.9–19.2)	Natural splines with 2, 3, or 4 df, compared goodness of fit using BIC. Log function of $PM_{2.5}$ ($\ln[PM_{2.5} + 1]$) yielded lower BIC than each of the spline models No evidence for departure from linearity. Natural spline model with 4 df had best model fit based on BIC
†Crouse et al. (2015) Canada–CanCHEC (Figures S3a)	Satellite-based methods (at postal code) 8.9; (1–18)	Restricted cubic spline functions with 2 df Natural spline fit was superior to linear model. Natural spline fit is supralinear (i.e., larger changes in risk for low concentrations compared to higher values)
†Di et al. (2017c) U.S.–Medicare (Figure 3, panel A)	Hybrid satellite-based methods, LUR, monitor; 1 × 1 km 11.5; (6.2–15.64 [5th–95th percentiles])	Examined potential of non-linear effects using a series of thin-plate splines and meta-smoothing Nearly linear with no signal of threshold down to 5 $\mu g/m^3$

Table 11-7(Continued): Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality.

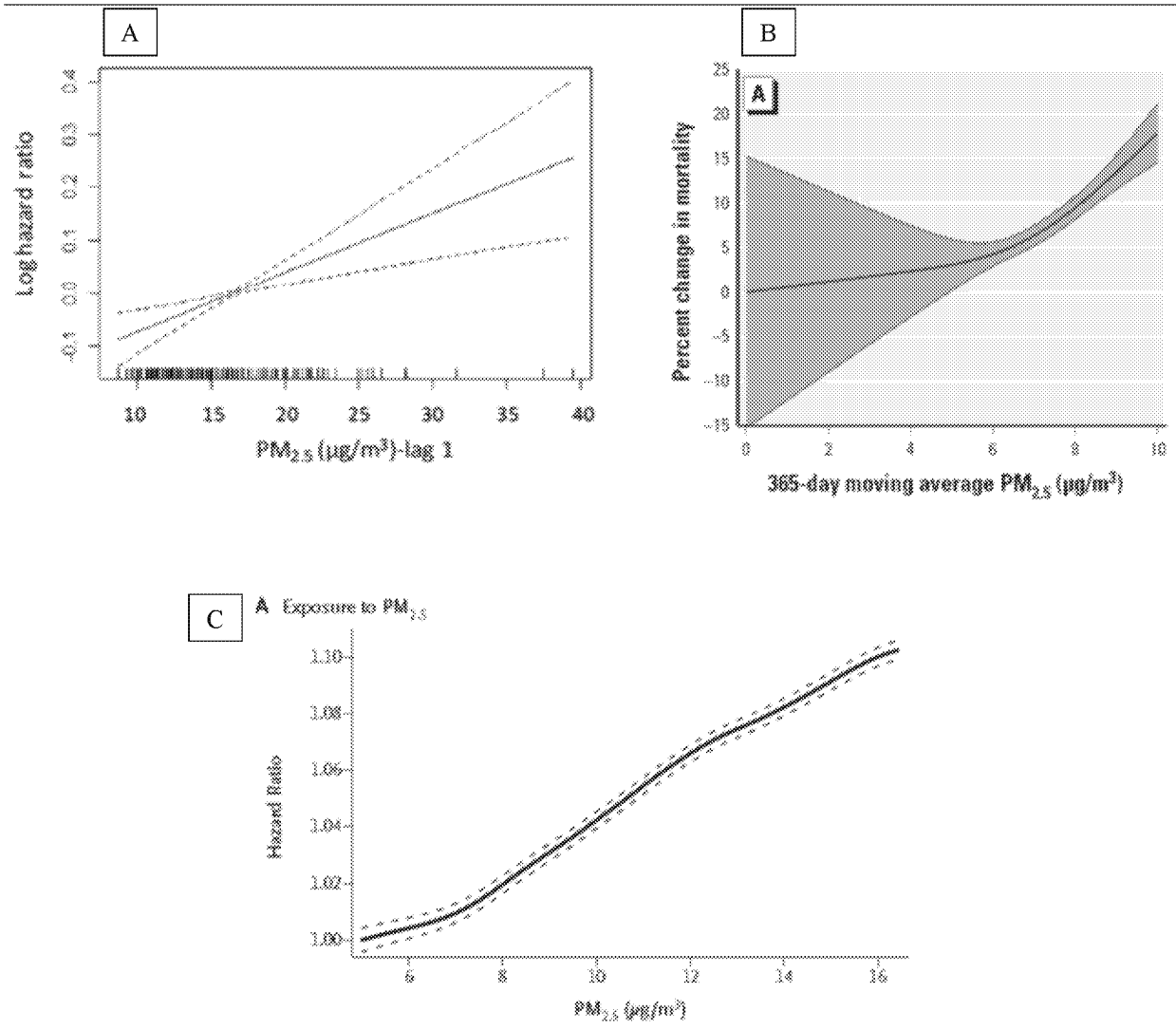
Study Location—Cohort Table/Figure from Reference	Exposure $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
†Hart et al. (2015) U.S.–Nurses' Health Study (Figures 1 and 2)	Spatio-temporal model; nearest monitor 12.0; (NR)	Comparison of mortality rates for a given $PM_{2.5}$ concentration (based on prediction from spatio-temporal model [Figure 1] or nearest monitor [Figure 2])
		Linear relationship for both spatio-temporal model and nearest monitor; Linear relationship for both uncorrected and measurement error-corrected mortality rates, slope steeper for measurement error-corrected exposure compared to uncorrected
†Lepeule et al. (2012) U.S.–HSC (Suppl. Figure 1)	Fixed-site monitor 15.9; (11.4–23.6)	Penalized spline models
		Linear relationship with exposures down to 8 $\mu g/m^3$. No evidence of a threshold. Highest confidence from 10–20 $\mu g/m^3$ based on greatest data density
†Pinault et al. (2016) Canada–CCHS (Figure 2)	Hybrid satellite-based methods, LUR, monitor 1 × 1 km 6.3; (0–13)	C-R: *R* package—"SmoothHR"; combination of AIC and BIC to determine optimal df; Threshold Analysis: newly defined exposure variables based on concentration corresponding to the largest log-likelihood value from the Cox model
		Linear relationship from 1.0–7.0 $\mu g/m^3$; slope is attenuated between 7.0 and 13.0 $\mu g/m^3$; Threshold concentration: 0 $\mu g/m^3$ (upper 95% CI 4.5 $\mu g/m^3$)
†Shi et al. (2015) U.S.–Medicare (Figure 3a)	Hybrid satellite-based methods, LUR, monitor; 1 × 1 km 8.12; (0.08, 20.22)	Penalized spline model (1.7 df) restricted to annual exposures <10 $\mu g/m^3$
		Linear relationship with evidence of an attenuated slope at concentrations <6 $\mu g/m^3$
†Thurston et al. (2015) U.S.–NIH–AARP (Figure 2)	Hybrid LUR geo-statistical model 12.2 (2.9–28.0)	Natural spline plots with 4 df (Referent HR = 1.0 at mean exposure level)
		Observed linear relationship
†Villeneuve et al. (2015) Canada–CNBSS (Figure 3)	Satellite-based methods (10 × 10 km) 9.1; (0.1–20.0)	C-R: Natural cubic spline functions with 3 df; Threshold analysis: newly defined exposure variables based on concentration corresponding to the largest log-likelihood value from the Cox model
		Non-linear V-shaped curve; Threshold analysis: best fitting model for a threshold at 11 $\mu g/m^3$

Table 11-7(Continued): Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality.

Study Location—Cohort Table/Figure from Reference	Exposure $PM_{2.5}$ Mean; Range in $\mu g/m^3$	Statistical Analysis Summary
†Wong et al. (2015) Hong Kong–Elderly Health Center (Figure 3)	Satellite-based methods (10 × 10 km) 35; (27–49)	Natural spline model (df not reported). Observed linear relationship, greatest certainty between 32 and 35 $\mu g/m^3$

AIC = Akaike Information Criterion; BIC = Bayesian information criterion; CanCHEC = Canadian Census Health and Environment Cohort; CCHS = Canadian Community Health Survey; CNBSS = Canadian National Breast Screening Study; df = degrees of freedom; EFFECT = Enhanced Feedback For Effective Cardiac Treatment; ESCAPE = European Study of Cohorts for Air Pollution Effects; HSC = Harvard Six Cities study; km = kilometer; LUR = land use regression; NIH-AARP = National Institutes of Health American Association of Retired Persons Diet & Health Cohort; NR = not reported; RoLS = Rome Longitudinal Study.

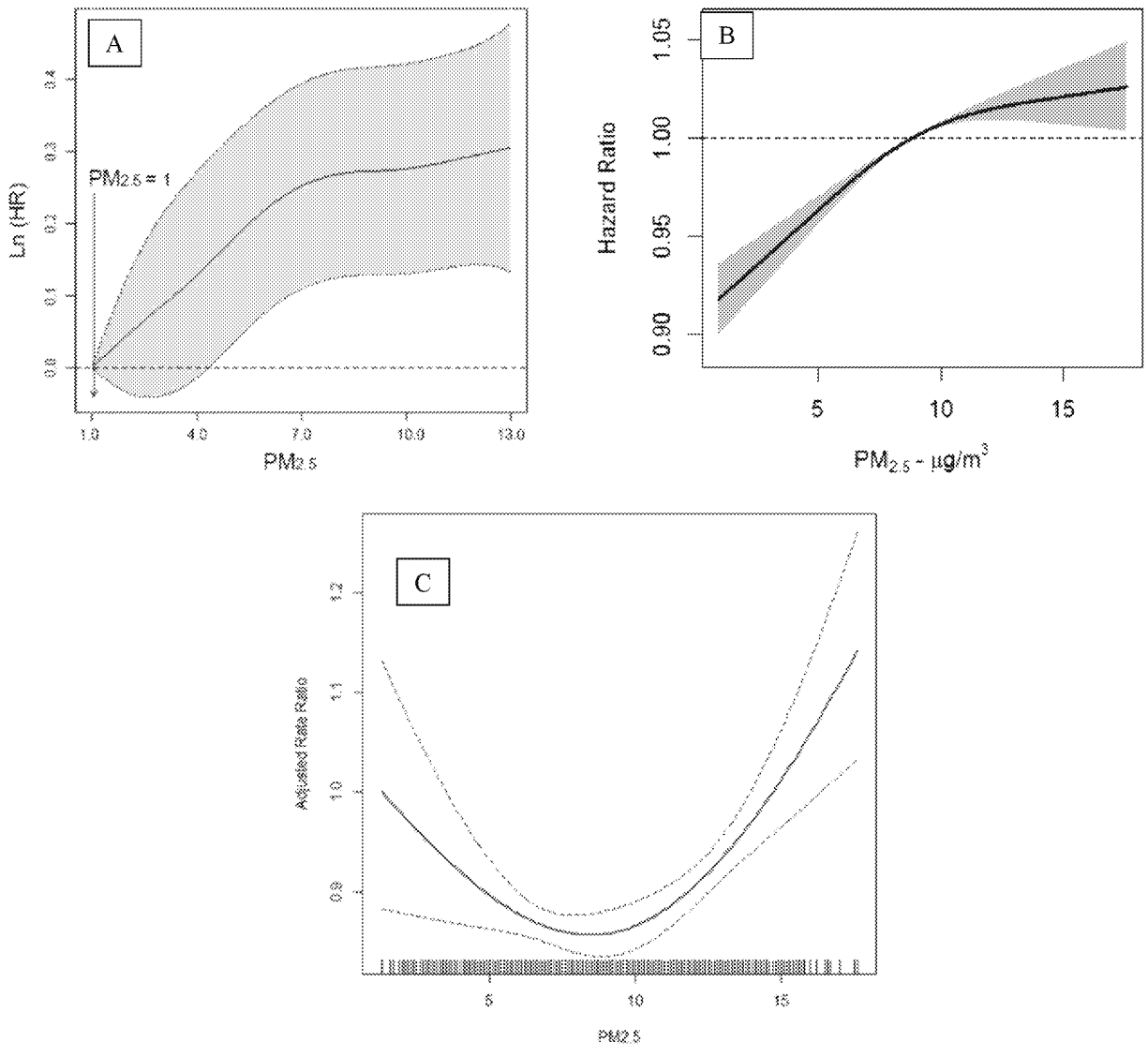
†Studies published since the 2009 PM ISA.



Note: Shaded areas or dotted lines indicate 95% confidence intervals. The tick marks on the *x*-axis identify the distribution of observations according to $PM_{2.5}$ concentrations.

Source: Permission pending, Panel A Lepeule et al. (2012); Panel B Shi et al. (2015); Panel C Di et al. (2017c)

Figure 11-22 Examples of concentration-response relationships between long-term $PM_{2.5}$ exposure and total (nonaccidental) or all-cause mortality in (A) the Harvard Six Cities Study using penalized splines (1974–2009); (B) long-term time-series study; (C) the Medicare Cohort using thin-plate spines.



Note: Shaded areas or dotted lines indicate 95% confidence intervals. The tick marks on the *x*-axis identify the distribution of observations according to $PM_{2.5}$ concentrations.

Source: Permission pending, Panel A Pinault et al. (2016); Panel B Crouse et al. (2015); Panel C Villeneuve et al. (2015).

Figure 11-23 Examples of concentration-response relationships between long-term $PM_{2.5}$ exposure and total (nonaccidental) mortality in (A) nonparametric estimates; (B) in the CanCHEC cohort study; (C) the Canadian National Breast Screening Study.

Rather than using splines to model the concentration-response relationship across a continuous range of $PM_{2.5}$ concentrations, Beelen et al. (2014a) conducted a cut-point analysis estimating the risk of long-term $PM_{2.5}$ exposure on total (nonaccidental) mortality when only participants with assigned $PM_{2.5}$ concentrations below 25, 20, 15, and 10 $\mu g/m^3$ were included in the model. The effect estimate was relatively unchanged when only participants with concentrations below 25 and 20 $\mu g/m^3$ were included in the model. Below 20 $\mu g/m^3$ the effect estimates remained positive but became less precise (i.e., wider 95% confidence intervals) as fewer observations were included in the model. The results of this cut-point analysis support the results of a spline model that evaluated the concentration-response relationship across the entire range of concentrations observed in the study area and found a generally linear association.

Overall, the majority of evidence continues to indicate a linear, no-threshold concentration-response relationship for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality, though some recent evidence indicates the possibility of a nonlinear concentration-response function. There is less certainty in the shape of the concentration-response curve at mean annual $PM_{2.5}$ concentrations generally below 8 $\mu g/m^3$, though some studies characterize the concentration-response relationship with certainty down to 4 $\mu g/m^3$.

11.2.5 Evaluation of Factors That May Influence $PM_{2.5}$ Associations

11.2.5.1 Comparison of Exposure Assessment Techniques

Recent studies have used a variety of both fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models) and satellite-based (e.g., aerosol optical depth [AOD] observations from satellites) methods, including hybrid methods that combine two or more fixed-site, model and/or satellite-based techniques to measure, estimate or predict $PM_{2.5}$ concentrations for use in assigning long-term $PM_{2.5}$ exposure in epidemiologic studies (see Section 3.3.2.4.3).

In a systematic comparison of fixed-site and satellite-based methods, Lee et al. (2011) concluded that, though observations were generally highly correlated, fixed-site measurements of $PM_{2.5}$ were more accurate than satellite-based observations of AOD when predicting concentrations within 98 km of the monitor, but that at distances greater than 98 km, satellite-based observations of AOD were better predictors of $PM_{2.5}$ concentrations (see Section 3.3.3 for details). In order to compare the use of fixed-site measurements and satellite-based observations of AOD, Jerrett et al. (2016) applied both methods to a common data set, the ACS cohort, and calculated effect estimates for circulatory and IHD mortality associated with $PM_{2.5}$ using both methods. They observed consistently positive associations between long-term $PM_{2.5}$ exposure and circulatory and IHD mortality, regardless of the exposure assessment technique used to assign exposure. However, they did note that when exposure assessment relied on satellite-based techniques, hazard ratios tended to be lower than when fixed-site measurements were used, or when fixed-site and satellite-based techniques were combined. Additionally, Jerrett et al. (2016)

combined all of the models into an ensemble model, weighted by model fit (i.e., AIC), and observed a 7.0% increase in circulatory mortality and a 7.5% increase in IHD mortality per 5 $\mu g/m^3$ increase in $PM_{2.5}$.

Hart et al. (2015) assigned exposure from the nearest fixed-site monitor as well as from a spatio-temporal model that included monitor observations, land use regression, and point-source emission density [see Yanosky et al. (2014) for details]. Effect estimates resulting from each exposure methods were nearly identical.

Alternately, Garcia et al. (2015) compared different exposure assessment techniques that all relied on observations from fixed-site monitors. Specifically, they evaluated assigning exposure based on the $PM_{2.5}$ concentration measured at the closest monitor, using inverse distance weighting (IDW) from multiple monitors, and by using a kriging model based on fixed-site monitor measurements. Exposure was assigned to ZIP code centroids by each exposure assessment technique. The results were consistent across exposure assessment techniques, with RRs ranging from 1.07 to 1.13 for CVD mortality, 1.20 to 1.28 for IHD mortality, and 1.01 to 1.03 for total (nonaccidental) mortality when considering the entire study area. Substantially more variability was observed for rural areas when analyses were stratified by urban and rural areas, with greater, though less precise (i.e., wider 95% confidence intervals), associations generally observed in rural areas.

A single study, Hart et al. (2015), used risk set regression calibration to correct for bias due to exposure measurement error resulting from differences in ambient concentrations and personal exposures to $PM_{2.5}$ in effect estimates for total (nonaccidental) mortality (see Section 3.4.5.2 for more detail on bias correction). They assumed that the "true" exposure was equal to the 12-month moving average for personal $PM_{2.5}$ exposure, and used percent difference in HRs ([("personal"—"ambient")/"personal"] × 100) to estimate the impact of exposure measurement error. They observed moderately higher HRs after adjusting for measurement error (1.18 vs. 1.13 from spatio-temporal exposure model; 1.22 vs. 1.12 from nearest monitor exposure model).

Overall, a number of studies demonstrate that the positive associations observed between long-term $PM_{2.5}$ exposure and mortality are robust to different methods of assigning exposure. In addition, a single study provides modest evidence that failing to correct for bias due to exposure measurement error could result in attenuated risk estimates.

11.2.5.2 Comparison of Statistical Techniques

Several recent studies have evaluated and compared the results of multiple statistical models in order to examine the robustness of the long-term $PM_{2.5}$ exposure-mortality relationship and to address concerns related to the sensitivity of results to model specification. In a reanalysis of the Harvard Six Cities study, Lepeule et al. (2012) evaluated a Cox proportional hazards model and a Poisson survival

analysis. The authors observed no substantial changes in results for the Cox models compared to the results from the Poisson survival analysis. Similarly, Thurston et al. (2016) evaluated both a traditional Cox proportional hazards model and a multilevel random-effects Cox proportional hazards model in analyses of the ACS cohort. The fully adjusted models included spatial random effects as well as contextual socio-economic variables. In addition, they examined models with random effects but not contextual variables, models with contextual variables but not random effects, and fixed effect models adjusted only for individual-level variables. The association between long-term exposure to $PM_{2.5}$ mass and IHD mortality was consistent across all of the models (HR ranged from 1.02 to 1.05). Estimates based on models without random effects and/or adjustment for contextual variables had more power and tended to be more precise. Similarities were observed in a different cohort, the NIH-AARP cohort (Thurston et al., 2015). Specifically, associations were more precise when contextual variables were not included, and the inclusion of random effects terms in the time independent Cox proportional hazards model resulted in associations similar to those observed from models without random effect terms. In an analysis of CVD mortality, Dehbi et al. (2016) used competing risk hazards regression models to allow for the influence of death from causes other than CVD. In addition, they used Cox modelling to verify that the observed results were not an artefact of using competing risk hazards regression models and observed similar results. Overall, these results from well-studied, highly regarded cohorts help to reduce uncertainties that the observed associations between long-term $PM_{2.5}$ exposure and mortality could be due to the statistical techniques employed or model specification, rather than a causal relationship.

11.2.5.3 Effects of Different Long-Term Exposure Windows

The delay between changes in exposure and changes in health has important policy implications. The 2009 PM ISA concluded that there was developing coherence in the evidence base that indicated that the health benefits from reducing air pollution could be expected within a few years of intervention (U.S. EPA, 2009). Several recent studies provide additional evidence to support this conclusion. Bentayeb et al. (2015) examined long-term exposure for four different averaging times: (1) annual mean exposure at baseline, (2) annual mean exposure 1 year before death, (3) yearly mean exposure during follow-up, and (4) average cumulative exposure from baseline through death or censure. Results for long-term $PM_{2.5}$ exposure and total (nonaccidental), cardiovascular and respiratory mortality were consistent for all four exposure windows examined. Lepeule et al. (2012) evaluated two exposure periods, 1 or 5 years before death or censure, and evaluated model fit using Akaike's Information Criterion (AIC). They observed the best fit for the 5-year exposure period. In additional sensitivity analyses, they allowed the exposure window to vary from 1 to 5 years before death or censure, and observed similar effect estimates to those in the main analysis. Using a different strategy, Wong et al. (2015) stratified the follow-up period to examine deaths occurring 2–4, 5–8, or ≥9 years after the baseline date. They observed greater risks for the period closest to the baseline date, though it is unclear if this is a result of a difference in the exposure window, or if it could be due to the age of the cohort. The cohort included participants aged 65 years or

older, and there is evidence indicating that risk decreases for individuals over 70 or 75 years of age. Thus, it is unclear if the greater risk observed for the early exposure window is due to the exposure window itself, or the age of participants during that exposure window. Overall, new evidence from recent studies continues to support the previous conclusion that health benefits from reducing air pollution could be expected with a few years of intervention.

11.2.6 Associations between $PM_{2.5}$ Sources and Components and Mortality

The 2009 PM ISA (U.S. EPA, 2009) included one study that examined the association between long-term exposure to $PM_{2.5}$ components and mortality (Lipfert et al., 2006). Integrating across health endpoints, the 2009 PM ISA concluded that there is not sufficient evidence to differentiate the components or sources more closely related to health outcomes when compared with $PM_{2.5}$ mass. A number of recent studies have examined the relationship between long-term exposure to PM components and mortality. A number of these studies estimate the risk associated with individual components of $PM_{2.5}$ (Figure 11-24), while others evaluate the potential for $PM_{2.5}$ composition to explain some of the regional/geographic heterogeneity observed in the risk estimates from studies of long-term $PM_{2.5}$ exposure.

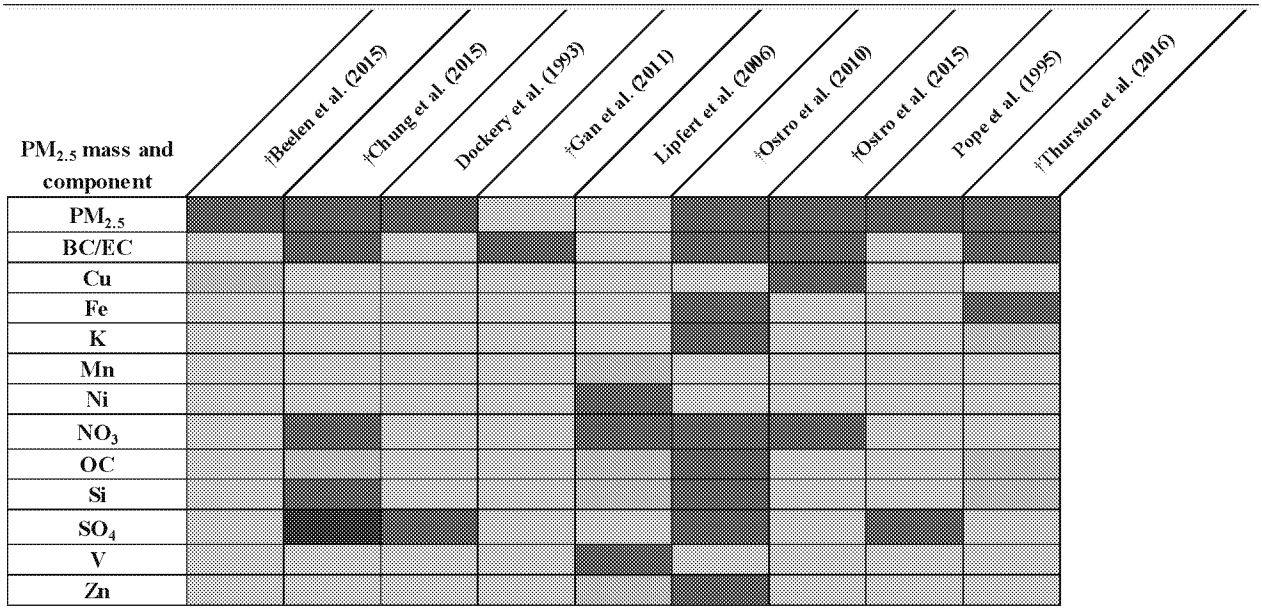
In an additional analysis of the CanCHEC cohort (described previously in Section 11.2.2.2), Crouse et al. (2016) used a novel method to calculate the risk of total (nonaccidental) and cardio-metabolic mortality associated with long-term exposure to $PM_{2.5}$ adjusted for the proportion of six individual $PM_{2.5}$ components (i.e., sulfate, nitrate, ammonium, OC, BC, dust). They observed that models of $PM_{2.5}$ mass alone were a better predictor of mortality than models of the combination of $PM_{2.5}$ mass and the proportion of any one of the six components they evaluated, but that models including the combination of $PM_{2.5}$ mass and the proportion of all six of the components were better predictors of mortality than models of $PM_{2.5}$ mass alone. In separate analyses of the CanCHEC cohort, authors collected $PM_{2.5}$ filters from 30 fixed-site monitors between 2012 and 2013 and evaluated the oxidative potential of the nonvolatile portion of $PM_{2.5}$ mass on the filter via antioxidant (glutathione and ascorbate) depletion tests (Weichenthal et al., 2016). When the $PM_{2.5}$ glutathione-related oxidative burden was estimated, the results were similar to those for $PM_{2.5}$ mass, though generally higher in magnitude. Generally null or negative hazard ratios were observed for all-cause and cause-specific mortality when $PM_{2.5}$ ascorbate-related oxidative burden was analyzed. Although not entirely consistent, these oxidative burden results may help to explain the potential for low concentrations of $PM_{2.5}$ to cause disease or to help explain geographic heterogeneity observed with $PM_{2.5}$-mortality associations.

A meta-analysis of European cohorts (i.e., the ESCAPE study, described previously in Table 11-6), evaluated mortality due to incident IHD events and eight different $PM_{2.5}$ components: S, K, Cu, Fe, Ni, V, Zn, and Si (Wolf et al., 2015). These authors used LUR to estimate $PM_{2.5}$ and component

concentrations, and cross validation of the models revealed variable performance, with some models performing poorly (i.e., $R^2 < 0.30$) and others performing moderately (i.e., $R^2 = 0.30–0.50$). The authors calculated single-component hazard ratios, as well as $PM_{2.5}$-adjusted hazard ratios, by regressing total PM on each component separately and then including the residual for each component in a model with total $PM_{2.5}$, using the estimate of the residual component to represent the independent component effect. Previous analyses of the ESCAPE cohort observed associations between long-term $PM_{2.5}$ exposure and CVD mortality. The results presented by Wolf et al. (2015) are consistent with these associations, and provide additional evidence for associations with K, Si and Fe, which could represent the resuspended road dust portion of $PM_{2.5}$. In sensitivity analyses where only cohorts for which the cross validation of the LUR model was ≥0.50, the results were relatively unchanged.

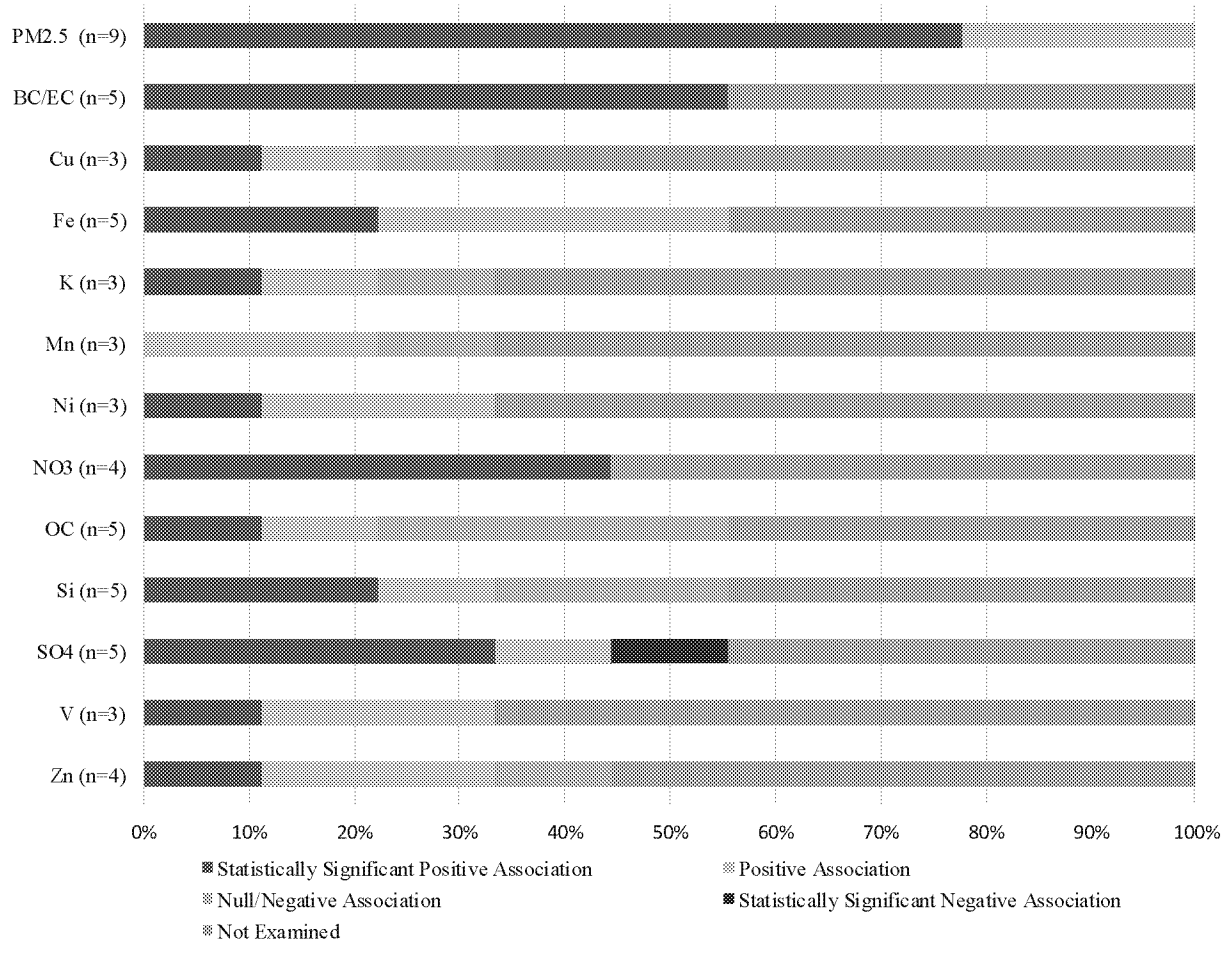
The evaluation of the association between $PM_{2.5}$ components and mortality is complicated by the different methods applied across studies. As a result, the systematic standardization of results across studies (i.e., per 5 $\mu g/m^3$ increase), as is the convention throughout this ISA, is not possible when evaluating results for $PM_{2.5}$ components. Overall, the results for individual $PM_{2.5}$ components across studies are generally more imprecise than the results for $PM_{2.5}$ (i.e., much wider confidence intervals, often including the null value), which make the individual results, as well as results across studies, more difficult to interpret. As such, for the purposes of characterizing results with respect to $PM_{2.5}$ components a different convention is employed to evaluate the pattern of associations across studies. Specifically, risk estimates from studies are classified into four categories in Figure 11-24 and Figure 11-25: (1) statistically significant positive associations; (2) positive associations, regardless of width of the confidence interval; (3) null or negative association; and (4) statistically significant negative association. Figure 11-24 and Figure 11-25 demonstrate consistent positive associations for total (nonaccidental) mortality and exposure to $PM_{2.5}$, BC/EC, Fe, Ni, NO_3^-, and V, with more studies evaluating $PM_{2.5}$, BC/EC and NO_3^-, and fewer studies examining the metals Fe, Ni, and V. Based on the pattern of results across this limited number of studies, it is difficult to disentangle the independent effect of any of these components from the effect of $PM_{2.5}$ mass.

Thurston et al. (2016) used source apportionment to evaluate the relationship between air pollution sources and IHD mortality in the ACS cohort. Sources were categorized based on source-identifier elemental tracers. They observed the strongest associations coal burning (HR: 1.05, 95% CI: 1.02, 1.08) and other combustion sources, and diesel traffic (HR: 1.03, 95% CI: 1.00, 1.06). Generally null associations were observed for other sources (i.e., wind-blown soil and biomass combustion). These results are generally consistent with previous studies of short-term exposure and mortality that have used source apportionment methods; previous studies have not considered long-term exposure and IHD mortality.



Note: †$PM_{2.5}$ component studies published since the 2009 PM ISA. Results are for total (nonaccidental) mortality except for Gan et al. (2011), who examine CVD mortality. Dark blue = study reported statistically significant positive association; Light blue = study reported a positive association regardless of width of confidence intervals; Light orange = study reported null or negative association; Red = study reported statistically significant negative association; Gray = study did not examine individual component. Only those $PM_{2.5}$ components that were examined in at least three studies are included in this figure.

Figure 11-24 Heat map of associations observed between $PM_{2.5}$ and $PM_{2.5}$ components and mortality.



n = number of studies that provided an estimate for $PM_{2.5}$ mass and individual $PM_{2.5}$ components.

Note: Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components detailed in Figure 11-24 that are statistically significant positive (dark blue), positive (light blue), null/negative (light orange), statistically significant negative (red), or not examined (gray).

Figure 11-25 Distribution of mortality associations for $PM_{2.5}$ and $PM_{2.5}$ components examined in studies detailed in Figure 11-24.

11.2.7 Summary and Causality Determination

Recent cohort studies evaluated since the completion of the 2009 PM ISA continue to provide consistent evidence of positive associations between long-term $PM_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mainly in North America and Europe. Many recent analyses further evaluated the association between long-term $PM_{2.5}$ exposures and the risk of mortality based on the original ACS study (Pope et al., 1995), adding new details about deaths due to cardiovascular disease (including IHD) and respiratory disease (including COPD), and extending the follow-up period of the ACS to 22 years (1982–2004). Adding to this evidence, recent U.S. and Canadian cohort studies

demonstrate consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality across various spatial extents, exposure assessment metrics, and statistical techniques, and locations, where mean annual average concentrations are ≤12 μg/m^3 (Section 11.2.2.2). Additionally, the evidence from recent studies reduce uncertainties related to potential copollutant confounding (Section 11.2.3) and continues to provide strong support for a linear, no-threshold C-R relationship (Section 11.2.4). The body of evidence for total mortality is supported by generally consistent positive associations with cardiovascular and respiratory mortality. There is coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) and biological plausibility for $PM_{2.5}$-related cardiovascular (Chapter 6) respiratory (Chapter 5) and metabolic (Chapter 7) disease, which supports the $PM_{2.5}$-mortality relationship. This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for long-term exposures to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 6-89.

The strongest evidence supporting the conclusion of a causal relationship between long-term $PM_{2.5}$ exposure and total mortality in the 2009 PM ISA was derived from analyses of the ACS and HSC cohorts. Recent extended analyses and reanalysis of these cohorts continues to support this relationship, demonstrating consistent positive associations for total (nonaccidental mortality) and across different cause-specific mortality outcomes. A recent series of analyses of the Medicare cohort of U.S. individuals provides additional support, culminating with the largest cohort study of nearly 61 million U.S. Medicare enrollees that reports positive associations with increases in $PM_{2.5}$ concentrations and stronger associations in areas where the mean annual $PM_{2.5}$ concentrations are ≤12 μg/m^3 (Di et al., 2017c). Another recent series of studies conducted in Canada provides results consistent with those of the Medicare cohort (i.e., positive associations between long-term $PM_{2.5}$ exposure and total mortality in areas where mean annual $PM_{2.5}$ concentrations are ≤12 μg/m^3. One difference between these studies is that the Canadian cohorts include all adults (aged 25+ years) and the Medicare cohort only includes adults aged 65+ years, demonstrating that these effects are not specific to one lifestage, but affect all adults. Also, an additional line of evidence is available that includes results from a number of cohorts that recruited subjects based on their place of employment, including female nurses, female teachers, male health professionals, and male truck drivers, which observe consistent, positive associations between long-term $PM_{2.5}$ exposure and total mortality.

Table 11-8 Summary of evidence for a causal relationship between long-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of the ACS and HSC cohorts, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.1	Mean concentrations across studies: 11.4–23.6 $\mu g/m^3$
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of the Medicare cohort, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean concentrations across studies: 8.12–12.0 $\mu g/m^3$
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple analyses of Canadian cohorts, with effect estimates similar in magnitude, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean concentrations across studies: 8.7–9.1 $\mu g/m^3$
	Positive associations between long-term $PM_{2.5}$ exposure and mortality in the multiple North American occupational cohorts, even after adjustment for common potential confounders.	Section 11.2.2.2	Mean concentrations across studies: 12.7–17.0 $\mu g/m^3$
	Positive associations with cardiovascular, respiratory, and lung cancer mortality.	Section 6.3.10.1	Mean (across studies): 4.1–17.9 $\mu g/m^3$
		Section 5.2.10	Mean (across studies): 4.1–17.9 $\mu g/m^3$
		Section 10.2.5.1	Mean (across studies): 6.1–33.7 $\mu g/m^3$

Table 11-8 (Continued): Summary of evidence indicating that a causal relationship exists between long-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	Positive associations observed between long-term $PM_{2.5}$ exposure and total mortality remain relatively unchanged after adjustment for O_3, NO_2 and $PM_{10-2.5}$ When reported, correlations with copollutants were highly variable (low to high).	Section 1.1.1.1; Figure 11-20; Figure 11-21	
Consistent positive epidemiologic evidence for associations between $PM_{2.5}$ exposure and total mortality across exposure measurement metrics	Positive associations consistently observed across studies that used fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models) and satellite-based (e.g., AOD observations from satellites) methods, including hybrid methods that combine two or more of these methods.	Section 11.2.2.6; Jerrett et al. (2016)	
Epidemiologic evidence supports a log-linear, no-threshold concentration-response (C-R) relationship	No evidence for deviation from linearity in several U.S. and Canadian cohorts	Section 11.2.2.4	

Table 11-8 (Continued): Summary of evidence indicating that a causal relationship exists between long-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Biological plausibility from studies of cardiovascular and respiratory morbidity and lung cancer incidence and mortality	Cardiovascular morbidity studies provide expanded body of evidence for associations between long-term $PM_{2.5}$ exposure and CHD, stroke and atherosclerosis, providing biological plausibility for a relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality.	Section 6.3 Miller et al. (2007) Chi et al. (2016)	Mean (across studies): 10.7–13.4 $\mu g/m^3$
	Respiratory morbidity studies provide some evidence for an association between long-term $PM_{2.5}$ exposure and development of COPD, providing limited biological plausibility for a relationship between long-term $PM_{2.5}$ exposure and respiratory mortality	Section 5.2.5	
	Consistent epidemiologic evidence for associations between $PM_{2.5}$ exposure and lung cancer incidence and mortality in cohort studies conducted in the U.S., Canada, Europe and Asia	Section 10.2.5.1 Figure 10-3	Mean (across U.S. and Canadian studies): 6.3–23.6 $\mu g/m^3$

ACS = American Cancer Society; AHSMOG = Adventist Health Study of Smog; AOD = aerosol optical depth; CO = carbon monoxide; EC = elemental carbon; HSC = Harvard Six Cities; MI = myocardial infarction; NLCS = Netherlands Cohort Study on Diet and Cancer; NO_2 = nitrogen dioxide; ppb = parts per billion; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Recent evidence helps to reduce uncertainties related to potential copollutant confounding of the relationship between long-term $PM_{2.5}$ exposure and mortality. Multiple studies evaluated ozone (Figure 11-20) and NO_2 (Figure 11-21) in copollutant models and observed similar hazard ratios for $PM_{2.5}$ regardless of whether ozone or NO_2 were included in the model. This supports an independent effect of long-term $PM_{2.5}$ exposure on mortality. Evidence for other potential copollutants (e.g., SO_2, CO) is limited.

Recent studies have used a variety of both fixed-site (i.e., monitors), model (e.g., CMAQ, dispersion models) and satellite-based [e.g., aerosol optical depth (AOD) measurements from satellites] methods, including hybrid methods that combine two or more fixed-site, model and/or satellite-based techniques to measure, estimate or predict $PM_{2.5}$ concentrations for use in assigning long-term $PM_{2.5}$ exposure in epidemiologic studies. Overall, the exposure assessment technique has had little influence on study results, with consistently positive associations of similar magnitude observed across studies using a variety of exposure assessment techniques. Notably, Jerrett et al. (2016) applied fixed-site measurements and satellite-based observations of AOD to a common data set, the ACS cohort, and calculated effect estimates for circulatory and IHD mortality associated with $PM_{2.5}$ using both methods. They observed consistently positive associations between long-term $PM_{2.5}$ exposure and mortality, regardless of the exposure assessment technique used to assign exposure. Additionally, Jerrett et al. (2016) combined multiple exposure assessment techniques into an ensemble model, weighted by model fit, and continued to observe similar positive associations with mortality. These results support an independent effect of long-term $PM_{2.5}$ exposure on mortality that is not overtly influenced by or a residual of the exposure assessment technique used in the study.

The number of studies examining the shape of the C-R function for long-term $PM_{2.5}$ exposure and mortality has substantially increased since the 2009 PM ISA. These studies used a number of different statistical techniques to evaluate the shape of the C-R function, including natural cubic splines, restricted cubic splines, penalized splines, thin-plate splines, and cut-point analyses (Table 11-7), and generally observe linear, no-threshold relationships down to 4–8 $\mu g/m^3$. Few studies have conducted extensive analyses exploring alternatives to linearity when examining the shape of the $PM_{2.5}$-mortality C-R relationship. Among these studies, there is some emerging evidence for a supra-linear C-R function, with steeper slopes observed at lower $PM_{2.5}$ concentrations. Though few, such supra-linear C-R functions are most commonly observed for cardiovascular mortality compared to total (nonaccidental) or respiratory mortality.

The 2009 PM ISA concluded that there is not sufficient evidence to differentiate the components or sources more closely related to health outcomes when compared with $PM_{2.5}$ mass, though the evidence for long-term exposure and mortality was limited. More recently, a number of studies examined the relationship between long-term exposure to PM components and mortality (Figure 11-24). Collectively, recent studies continue to demonstrate that no individual $PM_{2.5}$ component or source is a better predictor of mortality than $PM_{2.5}$ mass.

Overall, recent epidemiologic studies build upon and further reaffirm the conclusions of the 2009 PM ISA for total mortality. The evidence particularly from the assessment of $PM_{2.5}$-related cardiovascular and metabolic diseases, with more limited evidence from respiratory morbidity, provides biological plausibility for mortality due to long-term $PM_{2.5}$ exposures. In conclusion, the consistent positive associations observed across cohort studies conducted in various locations across North America are further supported by the results from copollutant analyses indicating robust associations independent of

O_3 and NO_2. **Collectively, this body of evidence is sufficient to conclude that a causal relationship exists between long-term $PM_{2.5}$ exposure and total mortality.**

11.3 Short-Term $PM_{10-2.5}$ Exposure and Total Mortality

The 2009 PM ISA concluded that the evidence is "suggestive of a causal relationship between short-term exposure to $PM_{10-2.5}$ and mortality" (U.S. EPA, 2009).[80] This evidence was based on generally consistent, positive associations across mortality outcomes from primarily single-city studies, with some additional evidence from a few multicity studies, conducted in the U.S. and Canada. However, there was uncertainty with respect to the associations observed across epidemiologic studies due to the different methods used to measure $PM_{10-2.5}$ concentrations, which included direct measurements of $PM_{10-2.5}$ using dichotomous samplers and calculating the difference between PM_{10} and $PM_{2.5}$ concentrations (e.g., at collocated monitors, taking the difference between area-wide averages of PM_{10} and $PM_{2.5}$). Compared to studies of $PM_{2.5}$, there were relatively few studies that conducted additional analyses to further examine the $PM_{10-2.5}$-mortality relationship, resulting in the inability to adequately assess potential copollutant confounding, as well as the influence of model specification, seasonal associations, and effect measure modification. Additionally, there was a lack of information on the chemical and biological components that comprise $PM_{10-2.5}$.

Since the completion of the 2009 PM ISA a number of new studies, with the majority being multicity, conducted in diverse geographic locations (e.g., U.S., Asia, and Europe) have examined the relationship between short-term $PM_{10-2.5}$ exposure and mortality. However, the relative number of studies focusing on short-term $PM_{10-2.5}$ exposure and mortality has remained small, with many of the studies still using rather crude approaches to estimating exposures to $PM_{10-2.5}$. As detailed in Section 11.2.1 on short-term $PM_{2.5}$ exposure and mortality, this section on $PM_{10-2.5}$ and mortality focuses primarily on multicity studies because they examine the association between short-term $PM_{2.5}$ exposure and a health effect over a large geographic area that consists of diverse atmospheric conditions and population demographics, using a consistent statistical methodology, which avoids the potential publication bias often associated with single-city studies (U.S. EPA, 2008). Other recent studies (i.e., single and multicity) that do not further inform uncertainties or limitations in the short-term $PM_{10-2.5}$ exposure and mortality evidence are not the focus of this section, and are available at: https://hero.epa.gov/hero/particulate-matter.

The following section provides a brief overview of the associations observed in recent studies of mortality and short-term $PM_{10-2.5}$ exposures, with the main focus on evaluating whether recent studies address the uncertainties and limitations identified in the 2009 PM ISA (U.S. EPA, 2009), specifically: copollutant confounding; model specification; effect modification (e.g., temperature, season); exposure

[80] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour average $PM_{10-2.5}$ concentrations, unless otherwise noted.

assessment; and the concentration-response relationship and related issues (e.g., lag structure of associations). The multicity studies discussed throughout this section, along with study-specific details, air quality characteristics, and the approach used to estimate $PM_{10-2.5}$ concentrations are highlighted in Table 11-9.

Table 11-9 Study-specific details and $PM_{10-2.5}$ concentrations from multicity studies in the 2009 PM ISA and 2004 PM air quality criteria document (AQCD), and recent multicity studies and meta-analyses.

Study	Mortality Outcome(s)	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Measurement of $PM_{10-2.5}$ Concentrations	Copollutant Examination
Klemm and Mason (2003)[a] Six U.S. cities (1979–1988)	Total	9.0[b]	75th: 15.5 Max: 30.1	$PM_{10-2.5}$ directly measured using dichotomous samplers[c]	Correlation (*r*): NA Copollutant models with: NA
Burnett and Goldberg (2003)[a] Eight Canadian cities (1986–1996)	Total	12.6	95th: 30.0 Max: 99.0	$PM_{10-2.5}$ directly measured using dichotomous samplers	Correlation (*r*): NA Copollutant models with: NA
Burnett et al. (2004) 12 Canadian cities (1981–1999)	Total	11.4	Max: 151.0	$PM_{10-2.5}$ directly measured using dichotomous samplers	Correlation (*r*): 0.27 NO_2 Copollutant models with: NO_2
Zanobetti and Schwartz (2009) 47 U.S. cities (1999–2005)	Total Cardiovascular Respiratory	11.8	98th: 40.2 99th: 47.2 Max: 88.3	$PM_{10-2.5}$ estimated by calculating difference between county-wide average PM_{10} and $PM_{2.5}$ concentrations	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$
†Malig and BD (2009) 15 California counties, U.S. (1999–2005)	Total Cardiovascular	12.3	75th: 13.7–52.8	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): −0.03–0.35 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$
†Janssen et al. (2013) Netherlands (2008–2009)	Total	7.7	75th: 9.5 Max: 53.9	$PM_{10-2.5}$ estimated by calculating difference between nationwide average of PM_{10} and $PM_{2.5}$ using 10 locations were both monitored	Correlation (*r*): 0.57 PM_{10}; 0.29 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$

Table 11-9 (Continued): Study-specific details and $PM_{10-2.5}$ concentrations from multicity studies in the 2009 PM ISA and 2004 PM AQCD, and recent multicity studies and meta-analyses.

Study	Mortality Outcome(s)	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Measurement of $PM_{10-2.5}$ Concentrations	Copollutant Examination
†Pascal et al. (2014) Nine French cities (2001–2006)	Total Cardiovascular Respiratory	7–9	Max: 25–83	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): <0.40 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$, O_3
†Samoli et al. (2013) Eight European Mediterranean cities (2001–2010)	Total Cardiovascular Respiratory	8.0–15.8[b]	75th: 12.0–20.3	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): 0.19–0.68 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$, NO_2, SO_2, O_3
†Lanzinger et al. (2016)[d] Five Central European cities (UFIREG) (2011–2014)	Total Cardiovascular Respiratory	4.7–9.8	Max: 21.6–44.6	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): 0.37–0.44 NO_2; 0.58–0.78 PM_{10}; 0.40–0.61 $PM_{2.5}$; 0.40–0.51 UFP; 0.50–0.58 PNC Copollutant models with: NA
†Stafoggia et al. (2017)[e] Eight European cities (1999–2013)	Total Cardiovascular Respiratory	5.0–16.0	NA	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at the same monitors	Correlation (*r*): 0.09–0.36 UFP Copollutant models with: NA
†Lee et al. (2015a) 11 East Asian cities (2001–2009)	Total Cardiovascular Respiratory	10.7–50.4[b]	75th: 15.4–82.5	$PM_{10-2.5}$ estimated by calculating difference between city-wide average of PM_{10} and $PM_{2.5}$ for each city	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$, O_3, SO_2, NO_2
†Chen et al. (2011) Three Chinese cities (CAPES) (2004–2008)	Total	49–101	---	$PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors	Correlation (*r*): 0.74–0.86 PM_{10}; 0.28–0.53 $PM_{2.5}$ Copollutant models with: $PM_{2.5}$

CAPES = China Air Pollution and Health Effects Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Multicity studies included in the 2004 PM AQCD.

[b]Median concentration.

[c]Until 1984 consisted of particles with aerodynamic diameter greater than 2.5 µm and less than 15 µm, and after first quarter 1984 upper end was less than 10 µm (Klemm et al., 2000).

[d]PM only measured in 4 of the 5 cities.

[e]Stafoggia et al. (2017) did not report quantitative estimates for cardiovascular and respiratory mortality.

†Studies published since the 2009 PM ISA.

11.3.1 Biological Plausibility for Short-Term $PM_{10-2.5}$ Exposure and Total Mortality

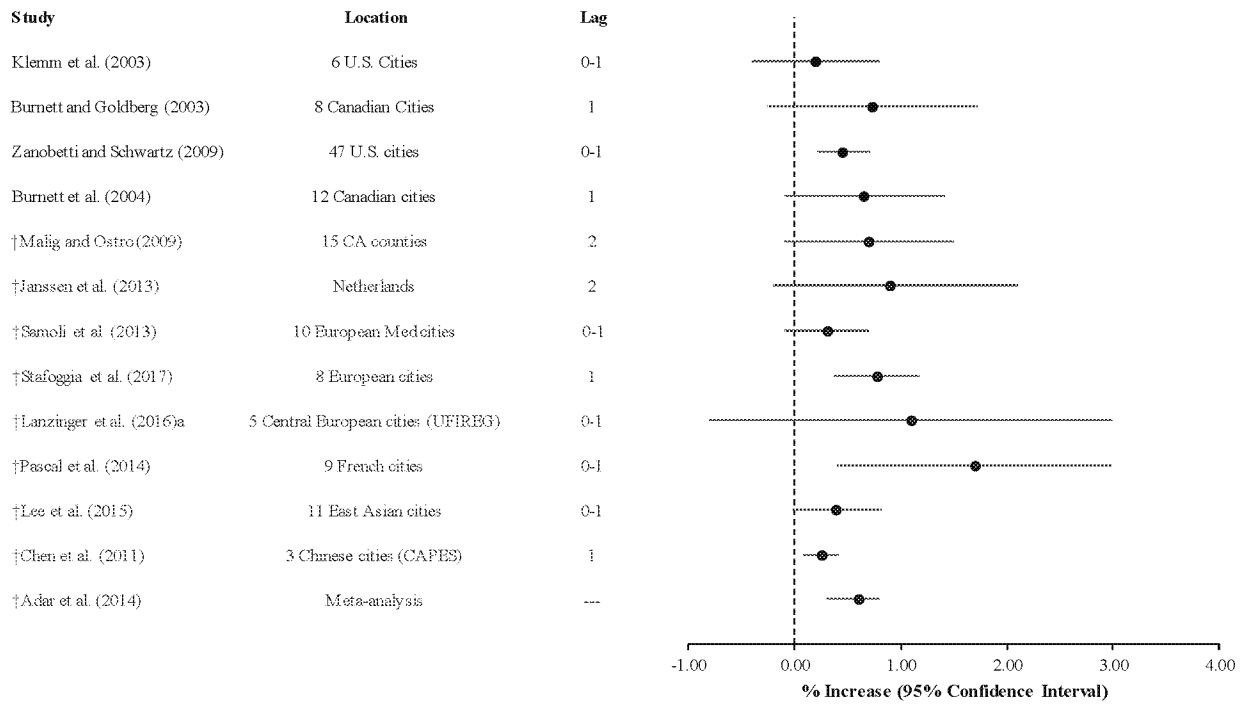
The preceding chapters characterized evidence related to evaluating the biological plausibility by which short-term $PM_{10-2.5}$ exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity (Section 6.3.1 and Section 5.3.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.3.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to $PM_{10-2.5}$ could result in initial events, such as an inflammatory response in the lungs, as well as systemic inflammation and altered hemostasis. Currently, evidence is lacking for progression to intermediate endpoints (e.g., endothelial dysfunction) and population outcomes (e.g., IHD, emergency department [ED] visits, and hospital admissions) that are observed in experimental and observational health studies. Similarly, Section 5.3.1 characterizes the available evidence by which inhalation exposure to $PM_{10-2.5}$ could progress from initial events to endpoints relevant to the respiratory system. There is some evidence for an initial event characterized by inflammatory responses that could support progression along an inflammation-mediated pathway. However, the evidence for how the initial events and subsequent endpoints could lead to increases in respiratory ED visits and hospital admissions is limited. Collectively, the progression demonstrated in the available evidence for cardiovascular and respiratory morbidity supports potential biological pathways by which short-term $PM_{10-2.5}$ exposures could result in cardiovascular and respiratory morbidity, but there is still uncertainty related to how these initial events could progress to more severe endpoints, including mortality.

11.3.2 Associations between Short-Term $PM_{10-2.5}$ Exposure and Total (Nonaccidental) Mortality in All-Year Analyses

Recent multicity studies that examined the relationship between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality have primarily been limited to Europe and Asia. The results from these studies, along with a meta-analysis, build on the relatively consistent, positive associations observed in multicity studies evaluated in the 2009 PM ISA and 2004 PM AQCD (Figure 11-26). It is worth noting that in the meta-analysis by Adar et al. (2014) an examination of publication bias indicated that estimates for $PM_{10-2.5}$ showed possible evidence of publication bias, which was not observed for $PM_{2.5}$ and may contribute to the small literature base for $PM_{10-2.5}$.

Consistent with the 2009 PM ISA, across studies different methods were used to measure $PM_{10-2.5}$ concentrations with most studies relying on some form of the difference method (i.e., subtracting PM_{10} concentrations from $PM_{2.5}$ concentrations) (Table 11-9). Although some studies have attempted to examine the relationship between different $PM_{10-2.5}$ monitoring methods as detailed in Section 2.4.2, these

analyses are limited to a few locations and it remains unclear how similar the absolute magnitude of $PM_{10-2.5}$ concentrations are across each method and whether the $PM_{10-2.5}$ concentrations estimated from each method are temporally correlated.



CAPES = China Air Pollution and Health Effects Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Only four of the five cities measured $PM_{2.5}$.

Note: †Studies published since the 2009 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Table S11-9 (U.S. EPA, 2018b).

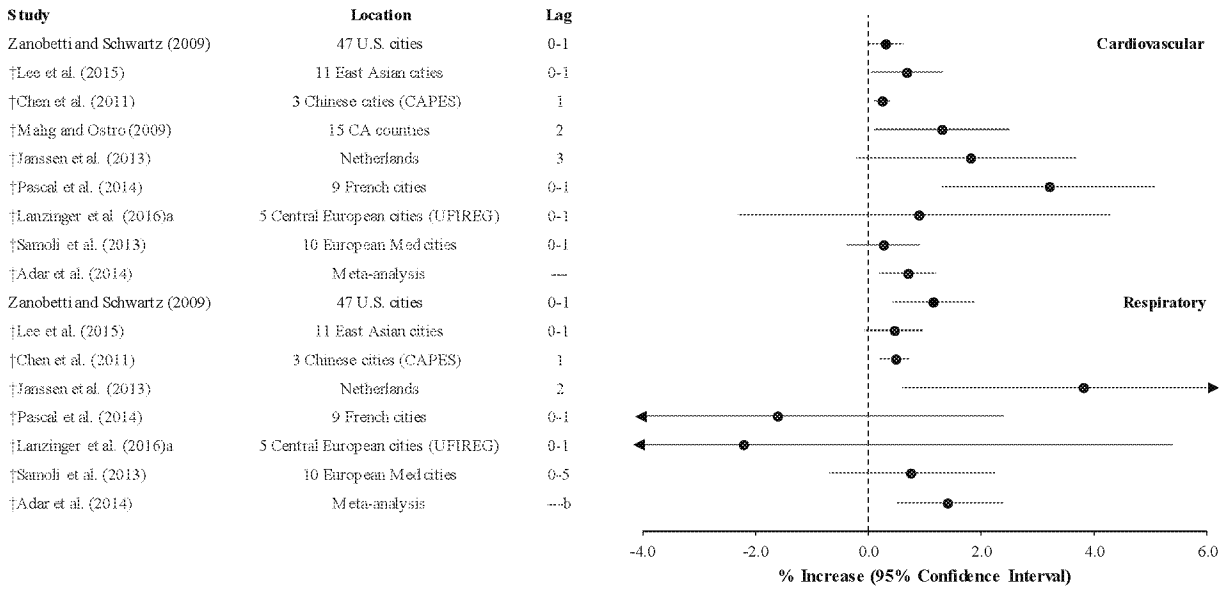
Figure 11-26 Summary of associations between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality in multicity studies for a 10 μg/m^3 increase in 24-hour average concentrations.

11.3.3 Associations between Short-Term $PM_{10-2.5}$ Exposure and Cause-Specific Mortality in All-Year Analyses

In addition to evaluating the relationship between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality a number of studies also evaluated cause-specific mortality (i.e., cardiovascular and respiratory mortality) (U.S. EPA, 2009). Studies that examined cardiovascular mortality reported

evidence of consistent positive associations. Fewer studies examined the association between short-term $PM_{10-2.5}$ exposure and respiratory mortality, with most, but not all studies reporting positive associations. Across both cardiovascular and respiratory mortality studies confidence intervals were larger than those observed for total (nonaccidental) mortality, which is a reflection of a majority of studies consisting of single-city studies.

Recent multicity studies add to the body of evidence detailed in the 2009 PM ISA (Figure 11-27). An examination of cardiovascular mortality finds evidence of consistent positive associations, but both the magnitude of the association along with the width of the 95% confidence intervals vary across studies. For respiratory mortality, most, but not all studies, reported evidence of positive associations. However, similar to the examination of cardiovascular mortality and short-term $PM_{10-2.5}$ exposures, the confidence intervals were large for some studies, particularly Janssen et al. (2013) and Lanzinger et al. (2016), which could be attributed to the rather short time-series for both studies.



CAPES = China Air Pollution and Health Effects Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Only four of the five cities measured $PM_{2.5}$, study included ages >1.

[b]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Note: †Studies published since the 2009 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Table S11-10 (U.S. EPA, 2018b).

Figure 11-27 Summary of associations between short-term $PM_{10-2.5}$ exposure and cardiovascular and respiratory mortality in multicity studies for a 10 µg/m^3 increase in 24-hour average concentrations.

11.3.4 Potential Confounding of the $PM_{10-2.5}$-Mortality Relationship

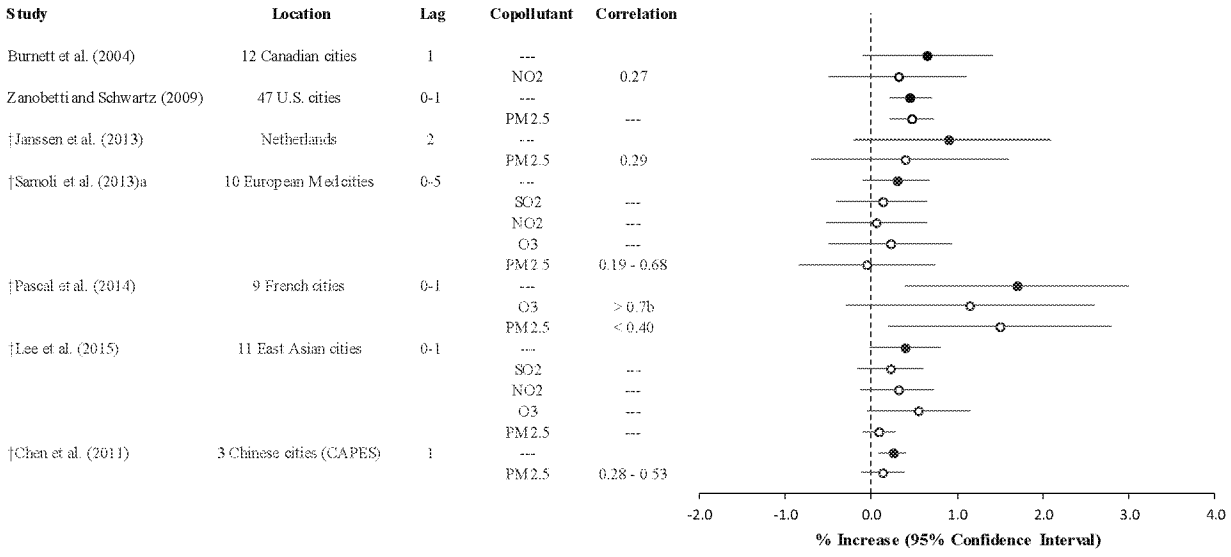
At the completion of the 2009 PM ISA, there was relatively little information on the potential confounding effects of other pollutants (i.e., both gaseous as well as $PM_{2.5}$) along with weather covariates on the $PM_{10-2.5}$-mortality relationship. As often detailed in air pollution epidemiology, a thorough evaluation of potential confounding by both copollutants and weather variables is important in understanding the relationship between an air pollutant exposure and health outcome.

11.3.4.1 Copollutants

Multicity studies that evaluated potential copollutant confounding in the 2009 PM ISA were limited to studies conducted by Zanobetti and Schwartz (2009) in 47 U.S. cities and Burnett et al. (2004)

in 12 Canadian cities, which examined copollutant models with $PM_{2.5}$ and NO_2, respectively. These studies provided initial evidence that $PM_{10-2.5}$-mortality associations remained positive in copollutant models with particles and gaseous pollutants although the $PM_{10-2.5}$ measurement methods varied between the studies (Figure 11-28). Recent multicity studies expand upon the limited number of studies evaluating the potential copollutant confounding of the $PM_{10-2.5}$-mortality relationship.

As summarized in Figure 11-28, copollutant models that included $PM_{2.5}$ resulted in $PM_{10-2.5}$-mortality associations that were often attenuated and generally remained positive in analyses conducted specifically in the U.S. and Canada, but in some cases became null (Samoli et al., 2013). This observation is supported by a study conducted in California that observed $PM_{10-2.5}$ mortality associations were similar in magnitude in copollutant models with $PM_{2.5}$ (quantitative results not presented) (Malig and BD, 2009). The indication that $PM_{10-2.5}$ results generally remain positive in copollutant models with $PM_{2.5}$, as presented in Figure 11-28, is supported by analyses that examined potential copollutant confounding in the context of a meta-analysis. When examining studies that conducted copollutant models with $PM_{2.5}$, Adar et al. (2014) observed that the $PM_{10-2.5}$-mortality association was similar in magnitude to that observed in single-pollutant models (quantitative results not provided). The results from copollutant models were further supported when stratifying $PM_{10-2.5}$-mortality estimates by the correlation with $PM_{2.5}$ (low, $r < 0.35$; medium, $r = 0.35$ to < 0.5; high, $r > 0.5$). The authors observed evidence of positive associations across each stratification, although the magnitude varied, with the association being largest in magnitude for correlations <0.35. Adar et al. (2014) further examined potential copollutant confounding by $PM_{2.5}$ through an analysis focusing on whether $PM_{10-2.5}$-mortality associations were present when the correlation between $PM_{2.5}$ and $PM_{10-2.5}$ increased and when $PM_{2.5}$ was also associated with mortality. As highlighted in Figure 11-29, there was not a consistent pattern of $PM_{10-2.5}$-mortality associations when there was also evidence of a $PM_{2.5}$-mortality association.



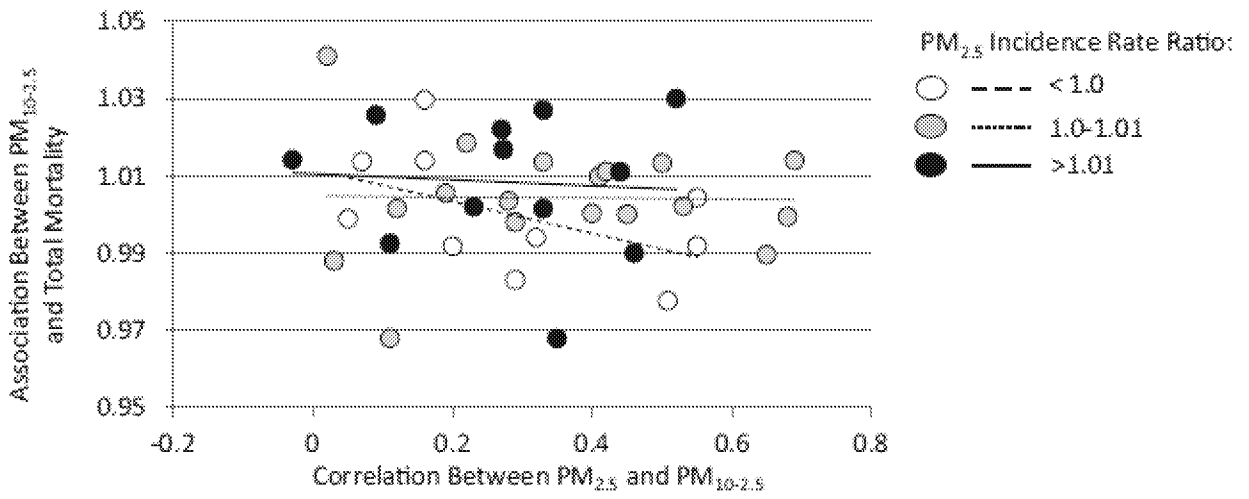
CAPES = China Air Pollution and Health Effects Study.

[a]Copollutant results only presented for a lag of 0–5 days.

[b]Correlation is for the summer across cities, no correlation was observed in all-year analyses.

Note: †Studies published since the 2009 PM ISA. Black circles = single-pollutant model. White circles = copollutant models. Corresponding quantitative results are reported in Supplemental Table S11-11 (U.S. EPA, 2018b).

Figure 11-28 Summary of associations between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality for a 10 µg/m^3 increase in 24-hour average concentrations in single and copollutant models from multicity studies.



Source: Permission pending, Adar et al. (2014).

Figure 11-29 Incidence rate ratios as a function of the correlation between short-term $PM_{10-2.5}$ and $PM_{2.5}$ concentrations stratified by $PM_{2.5}$ associations.

An evaluation of copollutant models including gaseous pollutants finds that in many instances the $PM_{10-2.5}$-mortality association is robust or slightly attenuated, but remains positive across studies (Figure 11-28). However, the interpretation of results across these studies is complicated by the relative lack of information on the correlation between $PM_{10-2.5}$ and gaseous pollutants.

Collectively, recent multicity studies provide additional information on whether the $PM_{10-2.5}$-mortality association is confounded by copollutants. However, uncertainty still remains, particularly with respect to the correlation between $PM_{10-2.5}$ and gaseous pollutants, which could further inform the copollutant model results observed across studies. Overall, there is some evidence that the $PM_{10-2.5}$-mortality association remains positive in copollutant models with $PM_{2.5}$ and O_3, with a more limited number of studies examining NO_2 and SO_2.

11.3.4.2 Long-Term Temporal Trends and Weather

The studies evaluated in the 2009 PM ISA that focused on the relationship between short-term $PM_{10-2.5}$ exposure and mortality did not conduct systematic evaluations or sensitivity analyses to examine the potential influence of model specification, specifically pertaining to the control for weather and temporal trends, on the $PM_{10-2.5}$-mortality association. Although a limited evaluation of model specification for the $PM_{10-2.5}$-mortality relationship has been conducted in a few recent multicity studies, compared to $PM_{2.5}$ (see Section 11.1.5.1) the overall evaluation remains rather limited.

Of the multicity studies that examined the influence of model specification, the focus has tended to be on adequate control for temporal trends. Lee et al. (2015a) in a study consisting of 11 East Asian countries examined the influence of altering the df per year to control for temporal trends from 6 to 12. The authors observed that as the df per year increased above 8 there was evidence that the $PM_{10-2.5}$ risk estimate was attenuated, but remained positive. The results of the systematic analysis of control for temporal trends in Lee et al. (2015a) may explain those observed in Samoli et al. (2013) where risk estimates were compared across models that selected 8 df/year to control for temporal trends a priori, used the absolute sum of the residuals of the partial autocorrelation function (PACF) to control for temporal trends, or conducted a case-crossover analysis, which inherently removes the need to control for temporal trends. The authors observed that the a priori method of selecting 8 df/yr resulted in the most conservative estimate of the $PM_{10-2.5}$-mortality association, which indicates that the results of Samoli et al. (2013) are comparable to those of Lee et al. (2015a). However, without knowing the df/yr selected through the PACF method it is unclear if the results between the two studies are consistent.

Only Pascal et al. (2014) in the study of nine French cities examined the influence of alternative weather covariates on the $PM_{10-2.5}$-mortality association. The authors used two distinct approaches: (1) a traditional analysis where daily mean temperature at lag 0 and lag 1−7 days was used instead of daily maximum and minimum temperature and (2) an alternative approach using a case crossover design where referent days were matched on days with the same temperature within the same month and year as the case day. Including a covariate for mean temperature instead of daily maximum and minimum temperature resulted in a dramatic reduction in the mortality risk estimate; whereas, when controlling for temperature using the case-crossover approach, the mortality risk estimate was almost identical to that obtained using the main generalized additive Poisson model.

Collectively, the studies that examined model specification indicate some potential sensitivity in $PM_{10-2.5}$-mortality risk estimates depending the number of df/yr included to control for temporal trends and the weather covariates included in the model. To date, however, the limited number of studies that examined the influence of model specification on the $PM_{10-2.5}$-mortality relationship do not allow for a full assessment of model specification and the potential sensitivity of risk estimates.

11.3.5 Effect Modification of the $PM_{10-2.5}$-Mortality Relationship

Relatively few studies have examined effect modification of the $PM_{10-2.5}$-mortality relationship. However, consistent with studies focusing on $PM_{2.5}$ and mortality, some studies examine whether specific individual- or population-level characteristics modify the $PM_{10-2.5}$-mortality association while other studies focus more broadly on examining those factors that potentially modify that $PM_{10-2.5}$-mortality association. The evaluation of individual- or population-level characteristics that may contribute to a population being at increased risk of PM-related health effects is detailed in Chapter 12. The following

section focuses exclusively on exploring those factors that may modify and further inform the relationship between short-term $PM_{10-2.5}$ exposure and mortality.

11.3.5.1 Season and Temperature

To date, few studies have conducted seasonal analyses to examine whether there is evidence that a specific season modifies the $PM_{10-2.5}$-mortality-relationship. Lee et al. (2015a) and Samoli et al. (2013) in studies of 11 East Asian cities and 10 European Mediterranean cities, respectively, focused on warm (April–September) and cold (October–March) season analyses. In Lee et al. (2015a), the authors observed a larger association during the cold season (0.71% [95% CI: 0.17, 1.3]; lag 0–1) compared to the warm season (0.16% [95% CI: −0.32, 0.64]). These results are the opposite of those observed in Samoli et al. (2013), although confidence intervals were large, associations were larger in magnitude in the warm season over the same lag period of 0–1 days (warm: 0.57% [95% CI: −0.16, 1.3]; cold: 0.26% [95% CI: −0.43, 0.95]). Instead of dividing the year into two seasons, Pascal et al. (2014) examined associations across the four seasons and reported seasonal associations more in line with the results of Samoli et al. (2013). The authors observed positive associations in the spring, summer, and autumn, with evidence of no association in the winter, with the summer and autumn having much larger associations, 4.6% (95% CI: 2.3, 6.9) and 3.3% (95% CI: 1.3, 5.1) at lag 0–1, respectively. Although Samoli et al. (2013) and Pascal et al. (2014) reported a relatively similar pattern of seasonal $PM_{10-2.5}$-mortality associations, the results from Lee et al. (2015a) complicate the interpretation of seasonal associations across studies.

In addition to examining seasonal associations, which in some respect are a proxy for examining the influence of temperature on the relationship between $PM_{10-2.5}$ and mortality, Pascal et al. (2014) also examined through a traditional stratified analysis if the $PM_{10-2.5}$-mortality association varied between warm (i.e., defined as days above the 97.5th percentile of the temperature distribution) and nonwarm days. The authors reported some evidence of a larger association on warm days (3.9% [95% CI: −3.3, 11.7]; lag 0–1) compared to nonwarm days (1.5% [95% CI: 0.3, 2.7]). These results were further reflected when examining the interaction ratio, which portrays the extra PM effect on warm days (1.04 [95% CI: 0.98, 1.12]).

Overall there is some evidence that warmer temperatures and seasons modify the $PM_{10-2.5}$-mortality association. However, the limited number of studies that examined both the potential modifying effects of season and temperature complicate the interpretation of results across studies.

11.3.5.2 Role of Exposure Assignment and Exposure Misclassification

Compared to $PM_{2.5}$, relatively few studies have examined the role of different parameters (e.g., distance to monitor) used to assign exposures on the $PM_{10-2.5}$ mortality relationship. Although

similar approaches to assign exposure have been used across PM size fractions, it remains unclear if different parameters impact the observed association and its magnitude. Malig and BD (2009) in the case-crossover study of 15 California counties examined the influence of reducing the buffer size around monitors from 20 to 10 km on the $PM_{10-2.5}$-mortality association when assigning exposure. The authors observed the strongest association at lag 2 when using the 20-km buffers (0.7% [95% CI: −0.1, 1.5]). When restricting the analysis to 10-km buffers around monitors, which reduced the number of cases examined by 40%, the results were almost identical (quantitative results not presented).

11.3.6 $PM_{10-2.5}$-Mortality Concentration-Response (C-R) Relationship and Related Issues

11.3.6.1 Lag Structure of Associations

Studies evaluated in the 2009 PM ISA that examined the relationship between short-term $PM_{10-2.5}$ exposure and mortality often selected lags to examine a priori and did not thoroughly examine the lag structure of associations. Across these studies positive associations were often observed with mortality at lags ranging from 0 to 1 day (U.S. EPA, 2009). Recent multicity studies provide additional insight on the lag structure of associations for short-term $PM_{10-2.5}$ exposure and mortality through systematic analyses focusing on both single- and multiday lags. As detailed in Section 11.1.8.1, the focus of this section is on those studies that conducted a systematic evaluation of different lags (e.g., single-day vs. distributed or average of multiple days) and include all single days evaluated in the distributed or multiday average lags (i.e., if a study examines a distributed or multiday average lag of 0−6 days it also examines single-day lags of 0 to 6 days).

Lee et al. (2015a) in the study of 11 East Asian cities examined the lag structure of associations for short-term $PM_{10-2.5}$ exposure and mortality by focusing on same-day exposure (lag 0) and multiday lags ranging from 0−1 to 0−4 days. Across this lag structure, the authors observed the strongest association, in terms of both magnitude and precision, at lag 0−1 and an association slightly smaller in magnitude across lags ranging from 0−2 to 0−4 days (quantitative results not presented). For each of the multiday lags; however, the confidence intervals were large. The pattern of associations observed in Lee et al. (2015a) is consistent with that reported in Stafoggia et al. (2017) in a study of eight European cities that examined single-day lags ranging from 0 to 10 days. The authors observed evidence of a positive association across lags 0 to 3 days, with the strongest association at lag 1 (quantitative results not presented).

Instead of focusing on single-day lags or a series of multiday lags, Samoli et al. (2013), in a study of 10 European Mediterranean cities, took a different approach to examining the lag structure of associations by focusing on distributed lags indicative of immediate (0−1), delayed (2−5), and prolonged

effects (0–5). The authors observed the strongest association at lag 0–1 (0.30% [95%: −0.10, 0.69]), with no evidence of an association at lags 2–5 and 0–5 days.

The results from studies that examined a series of single-day lags along with studies that examined multiday lags are consistent with the collective body of evidence detailed in the 2009 PM ISA. The combination of evidence from the 2009 PM ISA along with the limited number of studies that have systematically evaluated the lag structure of associations provide initial evidence indicating that mortality effects occur at lags ranging from 0 to 1 day.

11.3.6.2 Concentration-Response Relationship and Threshold Analyses

Studies evaluated in the 2009 PM ISA did not examine the C-R relationship and whether a threshold exists between short-term $PM_{10-2.5}$ exposure and mortality. Only the recent multicity study encompassing 10 European Mediterranean cities conducted by Samoli et al. (2013) provides some insight on the $PM_{10-2.5}$-mortality C-R relationship.

Similar to the analysis for $PM_{2.5}$ detailed in Section 11.1.10, Samoli et al. (2013) conducted a threshold analysis by selecting cutpoints at 5 $\mu g/m^3$ increments along the range of $PM_{10-2.5}$ concentrations from 0–20 $\mu g/m^3$. The authors assumed there was no risk of mortality below the defined threshold value. Samoli et al. (2013) did not observe any evidence of a threshold, which was reflected in the models with the lowest deviance being those that did not assume the presence of a threshold.

In understanding the relationship between short-term $PM_{10-2.5}$ exposure and mortality it is also important to characterize the relationship along the full distribution of ambient concentrations. Studies that examine the influence of extreme events can provide insight on the $PM_{10-2.5}$-mortality relationship at the high end of the $PM_{10-2.5}$ distribution. Lee et al. (2015a) in the analysis of 11 East Asian cities examined the influence of high particle concentrations on the $PM_{10-2.5}$-mortality association through an analysis focusing on (1) the highest 0.5% $PM_{10-2.5}$ concentrations and (2) dust storms. When including the highest 0.5% $PM_{10-2.5}$ concentrations in the analysis, the authors observed an attenuation of the $PM_{10-2.5}$ mortality association at lag 0–1 from 0.35% (95% CI: −0.02, 0.81) to 0.13% (95% CI: 0.01, 0.26). The authors reported a similar observation when examining associations between dust storm (0.07% [95% CI: −0.17, 0.31]; lag 0–1) and nondust storm (0.34% [95% CI: 0.05, 0.62]) periods, which collectively indicate a potential different relationship between short-term $PM_{10-2.5}$ exposure and mortality at higher particle concentrations. The results of Lee et al. (2015a) are supported by an analysis of areas with high $PM_{10-2.5}$ concentrations in the meta-analysis by Adar et al. (2014). When stratifying results by areas with mean concentrations <10 $\mu g/m^3$, 10 to <15 $\mu g/m^3$, and >15 $\mu g/m^3$, the authors observed the smallest associations for study areas with the highest mean $PM_{10-2.5}$ concentrations.

Summary

Although studies have not focused specifically on the shape of the $PM_{10-2.5}$-mortality C-R relationship, recent studies do not provide evidence of a threshold. Additionally, studies focusing on high concentrations provide initial evidence indicating that the shape of the C-R may plateau at higher concentrations; however, there are no statistically based analyses currently available that examine the shape of the C-R relationship to support the observations from these high concentration analyses.

11.3.7 Summary and Causality Determination

Since the completion of the 2009 PM ISA a number of multicity studies conducted primarily in Europe and Asia continue to provide evidence of consistent positive associations between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality. Although these studies contribute to increasing the confidence in the $PM_{10-2.5}$-mortality relationship, different methods are employed across studies in the measurement of $PM_{10-2.5}$ concentrations, which continues to form the main uncertainty in the associations observed and further support that the evidence is suggestive, but not sufficient to infer, a causal relationship. While uncertainty in the measurement of $PM_{10-2.5}$ remains, recent studies provide initial evidence that informs additional uncertainties and limitations identified in the studies evaluated in the 2009 PM ISA, specifically potential copollutant confounding; effect modification (e.g., temperature, season); and the shape of the C-R relationship and whether a threshold exists. The evidence for total mortality is supported by consistent positive associations with cardiovascular mortality with less consistent evidence for respiratory mortality; however, there is limited coherence and biological plausibility for cause-specific mortality when evaluating different health endpoints across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) for both cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity. This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for short-term exposures to $PM_{10-2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-10.

Table 11-10 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{10-2.5}$ concentrations.	Increases in mortality in multicity studies conducted in the U.S., Europe, and Asia Total mortality associations, supported by consistent increases in cardiovascular mortality with less consistent evidence for respiratory mortality in multicity studies conducted in the U.S., Europe, and Asia.	Section 11.3.2 Figure 11-26 Figure 11-27 Section 5.3.7 Section 6.3.8	Mean 24-h avg: U.S.: 12.3 Europe: 7–16 Asia: 10.7[d]–101 Table 11-1
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{10-2.5}$ association.	$PM_{10-2.5}$ associations are generally robust, but there are some instances of attenuation in copollutant models with gaseous pollutants and $PM_{2.5}$. However, there is limited information on the correlation between $PM_{10-2.5}$ and gaseous pollutants complicating the interpretation of results. Copollutant analyses with cardiovascular and respiratory mortality are limited to studies conducted in Europe and Asia and indicate that $PM_{10-2.5}$ associations generally remain positive, although attenuated in some instances. When reported, correlations with gaseous copollutants were primarily in the low ($r < 0.4$) to moderate ($r \geq 0.4$ or <0.7) range.	Section 11.3.4.1 Figure 11-28 Section 5.3.7.1.1 Figure 5-46 Section 6.3.8 Figure 6-32	
Uncertainty regarding exposure measurement error	Across studies $PM_{10-2.5}$ concentrations are measured using a number of approaches (i.e., directly measured from dichotomous sampler, different between PM_{10} and $PM_{2.5}$ at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared in terms of whether they have similar spatial and temporal correlations.	Table 11-9 Section 3.3.1.1	
Epidemiologic evidence provides some support for a no-threshold concentration-response (C-R) relationship.	Initial evidence from a study conducted in Europe for a no-threshold relationship, while a study conducted in Asia along with a meta-analysis indicating that the shape of the C-R curve may be different at higher concentrations.	Section 11.3.6.2	

Table 11-10 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Limited biological plausibility from cardiovascular and respiratory morbidity evidence.	Cardiovascular morbidity studies provide some evidence for ischemic events from epidemiologic studies, but limited experimental evidence resulting in limited coherence and biological plausibility for $PM_{10-2.5}$-related cardiovascular effects. Collectively, there is limited biological plausibility to support a relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular mortality, which comprises ~33% of total mortality.[e] Respiratory morbidity studies provide some evidence for effects on pulmonary inflammation and function, which is supported by asthma-related hospital admissions and ED visits, but overall there is limited coherence and biological plausibility for $PM_{10-2.5}$-related respiratory effects. Collectively, there is limited biological plausibility to support a relationship between short-term $PM_{2.5}$ exposure and respiratory mortality, which comprises ~9% of total mortality.[e]	Section 6.3.13 Table 6-58 Section 5.3.8 Table 5-37	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015b).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

[d]Median concentration from Lee et al. (2015a).

[e]Statistics taken from NHLBI (2017).

The evidence from recent multicity studies of short-term $PM_{2.5}$ exposures and mortality demonstrates consistent positive associations with total (nonaccidental) mortality, with increases ranging from 0.25% (Chen et al., 2011) to 1.70% (Pascal et al., 2014) at lags of 0 to 2 day in single-pollutant models. However, across studies different approaches have been employed to measure $PM_{10-2.5}$ concentrations (i.e., directly measured from a dichotomous sampler, difference between PM_{10} and $PM_{2.5}$ at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared to determine if their spatial and temporal correlation are similar, contributing uncertainty to the comparison of results across studies (Section 2.4, Section 3.3.1). Recent studies expand the assessment of potential copollutant confounding of the $PM_{10-2.5}$-mortality relationship, and provide some evidence that $PM_{10-2.5}$ associations remain positive in copollutant models, but there is some evidence that associations are attenuated (Section 11.3.4.1). Overall, the assessment of potential copollutant confounding is limited due to the lack of information on the correlation between $PM_{10-2.5}$ and gaseous

pollutants and the small number of locations in which copollutant analyses have been conducted. Analyses of cause-specific mortality provide some supporting evidence for total (nonaccidental) mortality associations, but overall estimates are more uncertain (i.e., wider confidence intervals) and less consistent, specifically for respiratory mortality (Figure 11-27). For both cardiovascular and respiratory mortality there was a limited assessment of potential copollutant confounding, with the pattern of associations and uncertainties similar to those observed for total (nonaccidental) mortality. The assessment of cardiovascular (Chapter 6) and respiratory morbidity (Chapter 5) provides limited biological plausibility for $PM_{10-2.5}$-related cardiovascular and respiratory mortality.

In addition to examining potential copollutant confounding, a few studies also assessed whether statistical models adequately account for temporal trends and weather covariates. To date, this assessment remains limited, but initial evidence indicates that $PM_{10-2.5}$ associations may be sensitive to model specification. An examination of whether associations vary by season and temperature provide some evidence that $PM_{10-2.5}$-mortality associations are larger in magnitude during warmer temperatures and seasons, but this pattern was not evident across all studies (Section 11.3.5.1). Across the studies evaluated, a few conducted systematic evaluations of the lag structure of associations. These studies examined either a series of single-day lags or whether there was evidence of an immediate (lag 0−1), delayed (lag 2−5), or prolonged effect (lag 0−5), and provided initial evidence that the $PM_{10-2.5}$ is immediate (i.e., lags 0 to 1 day) (Section 11.3.6.1). At the completion of the 2009 PM ISA no studies had assessed the $PM_{10-2.5}$-mortality C-R relationship, and recent studies have only conducted cursory analyses that do not thoroughly inform the shape of the C-R curve or whether a threshold exists.

Overall, recent epidemiologic studies provide additional support of consistent positive associations between short-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality, but there remains a large degree of uncertainty due to the various approaches used to measure $PM_{10-2.5}$ concentrations. The lack of information on the spatial and temporal correlation between the various measurement approaches reduces the confidence in the associations observed across studies. Additionally, the evidence from the assessment of short-term $PM_{10-2.5}$ exposures and cardiovascular and respiratory morbidity provide limited biological plausibility for $PM_{10-2.5}$-related mortality. Although recent studies attempt to address previously identified uncertainties and limitations in the $PM_{10-2.5}$-mortality relationship, the overall assessment of potential copollutant confounding, model specification, the lag structure of associations, and the C-R relationship remains limited. **Collectively, this body of evidence is suggestive, but not sufficient to infer, that a causal relationship exists between short-term $PM_{10-2.5}$ exposure and total mortality.**

11.4 Long-Term $PM_{10-2.5}$ Exposure and Total Mortality

The 2009 PM ISA reported that the evidence was "limited to adequately characterize the association" between long-term $PM_{10-2.5}$ exposure and mortality (U.S. EPA, 2009), noting that findings

from the AHSMOG (Chen et al., 2005; McDonnell et al., 2000) and Veterans (Lipfert et al., 2006) cohorts provided limited evidence for an association, especially after adjustment for $PM_{2.5}$ in the models. Each of these studies subtracted $PM_{2.5}$ concentrations from PM_{10} concentrations to calculate a concentration for $PM_{10-2.5}$, contributing to uncertainty in their interpretation. Due to the dearth of studies examining the association between long-term $PM_{10-2.5}$ exposure and mortality, the 2009 PM ISA concluded that the evidence was "inadequate to determine if a causal relationship exists" (U.S. EPA, 2009).[81] Recent studies provide some additional evidence to inform the relationship between long-term $PM_{10-2.5}$ exposure and mortality, though they often have similar limitations to those noted for studies included in the 2009 PM ISA.

11.4.1 Biological Plausibility for Long-Term $PM_{10-2.5}$ Exposure and Total Mortality

The preceding chapters characterized evidence related to evaluating the biological plausibility by which long-term $PM_{10-2.5}$ exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity and metabolic disease (Section 6.4.1, Section 5.4.1, and Section 7.4.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.4.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to $PM_{10-2.5}$ could result in initial events, such as an inflammatory response in the lungs, and limited evidence for altered hemostasis and arterial thrombosis. Arterial thrombosis can progress to IHD and thus provides a plausible mechanism by which ED visits and hospital admissions related to IHD can occur. Similarly, Section 5.4.1 characterizes the available evidence by which inhalation exposure to $PM_{10-2.5}$ could progress from initial events to endpoints relevant to the respiratory system. This includes evidence for markers of oxidative stress and inflammation and enhanced allergen-induced responses and airway changes that could play a role in asthma development and/or exacerbation. However, the evidence for how the initial events and subsequent endpoints could lead to the observed increases in respiratory ED visits and hospital admissions is limited. Section 7.4.1 outlines the limited evidence for an initial event (i.e., pulmonary inflammation) that could initiate mechanisms by which inhalation exposure to $PM_{10-2.5}$ could progress to intermediate endpoints and eventually result in population outcomes such as metabolic disease. However, the evidence for how pulmonary inflammation could lead to metabolic disease is limited. Collectively, the progression demonstrated in the available evidence for cardiovascular and respiratory morbidity and metabolic disease provides limited support for potential biological pathways by which long-term $PM_{10-2.5}$ exposures could result in mortality.

[81] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{10-2.5}$ concentrations, unless otherwise noted.

11.4.2 Associations between Long-Term $PM_{10-2.5}$ Exposure and Mortality

Several recent U.S. cohort studies examined the association between long-term $PM_{10-2.5}$ exposure and mortality in cohorts for which subjects were recruited based on their place of employment. Puett et al. (2009) examined the association between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality among a cohort of female nurses in the Nurses' Health Study from 13 states in the Northeast and Midwest from 1992 through 2002. Spatio-temporal models were used to assign exposure to $PM_{2.5}$ and PM_{10}, and the $PM_{10-2.5}$ concentrations were derived via subtraction. The authors observed positive associations with total (nonaccidental) and CHD mortality, with the strongest association observed for fatal CHD events. These associations were attenuated to below the null value in copollutant models that include $PM_{2.5}$. Using a design similar to that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term $PM_{10-2.5}$ (derived by subtraction of $PM_{2.5}$ from PM_{10}) exposure and mortality among men enrolled in the Health Professionals cohort. Near null associations were observed for both total (nonaccidental) and CHD mortality in this cohort.

A European pooled-analysis combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) (Beelen et al., 2014a), cardiovascular (Beelen et al., 2014b), and respiratory (Dimakopoulou et al., 2014) mortality. LUR models were used to assign exposure to $PM_{2.5}$ and PM_{10}, and the $PM_{10-2.5}$ concentrations were derived via subtraction. The authors applied a common statistical protocol to data from each of the 22 cohorts, from 13 different European countries, in the first stage of the analysis and combined the cohort-specific effects in a second stage. The authors observed a near-null association between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) (Beelen et al., 2014a), cardiovascular (Beelen et al., 2014b), and respiratory (Dimakopoulou et al., 2014) mortality. The strongest association was observed for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.17, 95% CI: 0.9, 1.52) (Beelen et al., 2014b), though copollutant models with $PM_{2.5}$ were not reported for this comparison. Using the same exposure models used for the pooled cohort study, Dehbi et al. (2016) assigned $PM_{10-2.5}$ exposure to two British cohort studies that were pooled together to examine CVD mortality. The British cohorts included follow-up between 1989 and 2015, though $PM_{10-2.5}$ exposure estimates were available for 2010–2011. The authors observed a negative association when exposure was considered on the continuous scale, but positive associations for each quartile when exposure was categorized. However, the confidence intervals were wide and overlapping for all of the results, and the inconsistency may indicate generally null results, but instability in the model. In a separate European cohort, Bentayeb et al. (2015) used the CHIMERE chemical transport model to estimate PM_{10} and $PM_{2.5}$, and then subtracted to estimate long-term $PM_{10-2.5}$ exposure. The authors observed positive association with total (nonaccidental), cardiovascular, and respiratory mortality, though the association with total (nonaccidental) mortality was attenuated in copollutant models with $PM_{2.5}$. The associations with cardiovascular and respiratory mortality were not evaluated in copollutant models.

Recent studies are characterized in Table 11-11. While there are more studies available in this review that examine the association between long-term $PM_{10-2.5}$ exposure and mortality, the body of evidence remains limited. In addition, to date all of the studies that have examined the relationship between long-term $PM_{10-2.5}$ exposure and mortality have used the difference method to derive concentrations for $PM_{10-2.5}$, contributing to the uncertainty associated with these effect estimates. Overall, there is no consistent pattern of associations for total, cardiovascular, or respiratory mortality. In the instances where positive associations were observed for long-term $PM_{10-2.5}$ exposure and mortality, and $PM_{2.5}$ copollutant model results were reported, the $PM_{10-2.5}$ effect estimates were often attenuated but still positive after adjusting for $PM_{2.5}$.

Table 11-11 Epidemiologic studies of long-term exposure to $PM_{10-2.5}$ and mortality.

Study	Cohort Location	Mean $PM_{10-2.5}$ µg/m³	Exposure assessment	Single Pollutant Hazard Ratio[a] 95% CI	Copollutant Examination
McDonnell et al. (2000)	AHSMOG (U.S.)	27.3	ZIP code average Subtraction method	Total (men): 1.03 (0.96, 1.10) Resp (men): 1.09 (0.94, 1.28) Lung Cancer (men): 1.12 (0.79, 1.60)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total (men): 0.99 (0.91, 1.08) $PM_{2.5}$: Resp (men): 1.03 (0.86, 1.24)
Chen et al. (2005)	AHSMOG (U.S.)	25.4	ZIP code average Subtraction method	CHD (men): 0.96 (0.81, 1.14) CHD (women): 1.17 (0.98, 1.40)	Correlation (*r*): NA Copollutant models with: NA
Lipfert et al. (2006)	Veterans (U.S.)	16	County average Subtraction method	Total (men): 1.03 (1.01, 1.05)	Correlation (*r*): NA Copollutant models with: NA
†Puett et al. (2009)	Nurses' Health (U.S.)	7.7	Spatio-temporal models Subtraction method	Total (women): 1.01 (0.94, 1.09) CHD (women): 1.07 (0.85, 1.33)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total (women): 0.98 (0.91, 1.06) $PM_{2.5}$: CHD (women): 0.95 (0.75, 1.22)
†Puett et al. (2011)	Health Professionals (U.S.)	10.1	Spatio-temporal models Subtraction method	Total (men): 0.95 (0.89, 1.03) CHD (men): 1.03 (0.90, 1.18)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total (men): 0.98 (0.90, 1.06) $PM_{2.5}$: CHD (men): 1.05 (0.90, 1.22)

Table 11-11 (Continued): Epidemiologic studies of long-term exposure to $PM_{10-2.5}$ and mortality.

Study	Cohort Location	Mean $PM_{10-2.5}$ µg/m^3	Exposure assessment	Single Pollutant Hazard Ratio[a] 95% CI	Copollutant Examination
†Beelen et al. (2014a)	ESCAPE (Europe)	4.0–20.7	LUR models Subtraction method	Total: 1.04 (0.98, 1.10)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total: 1.01 (0.92, 1.11)
†Beelen et al. (2014b)	ESCAPE (Europe)	4.0–20.7	LUR models Subtraction method	CVD: 1.02 (0.91, 1.13) IHD: 0.92 (0.77, 1.11) MI: 0.88 (0.71, 1.10) CBVD: 1.17 (0.90, 1.52)	Correlation (*r*): NA Copollutant models with: NA
†Dimakopoulou et al. (2014)	ESCAPE (Europe)	4.0–20.7	LUR models Subtraction method	Resp: 0.95 (0.76, 1.14)	Correlation (*r*): NA Copollutant models with: NA
†Dehbi et al. (2016)	2 British Cohorts	6.4	Same exposure as ESCAPE	CVD: 0.94 (0.56, 1.60)	Correlation (*r*): NA Copollutant models with: NA
†Bentayeb et al. (2015)	Gazel (France)	8.0	CHIMERE chemical transport model Subtraction Method	Total: 1.22 (1.09, 1.37) CVD: 1.32 (0.89, 1.91) Resp: 1.27 (0.96, 1.72)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: Total: 1.07 (0.85, 1.37)

[a]Hazard Ratio of mortality per 5 µg/m^3 change in $PM_{10-2.5}$.

†Studies published since the 2009 PM ISA.

11.4.3 Summary and Causality Determination

Since the completion of the 2009 PM ISA a number of recent cohort studies conducted primarily in the U.S. and Europe provide no consistent evidence for positive associations between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality. In addition to the inconsistent results, all of the studies use the difference of PM_{10} and $PM_{2.5}$ (measured at monitors or estimated from models) to estimate $PM_{10-2.5}$, which continues to be a main uncertainty in the positive associations that are observed in some cohorts and further support that the evidence is suggestive of, but not sufficient to infer, a causal relationship. An additional uncertainty is related to potential copollutant confounding; positive associations observed in the Nurses' Health Study (Puett et al., 2009), AHSMOG (McDonnell et al., 2000) and ESCAPE (Beelen et al., 2014a) cohorts were attenuated to the null when $PM_{2.5}$ was included in the model. The strongest evidence for total mortality comes from the GAZEL cohort (Bentayeb et al., 2015) in France; the authors observed a 22% increase in total mortality associated with increases in $PM_{10-2.5}$. This association remained positive in copollutant models with $PM_{2.5}$, but was attenuated and less precise. There is limited information on biological plausibility and limited coherence across scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) for cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity and metabolic disease (Chapter 7). This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for long-term exposures to $PM_{10-2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-12.

Overall, recent epidemiologic studies provide inconsistent evidence for positive associations between long-term $PM_{10-2.5}$ exposure and total (nonaccidental) mortality. A positive association between long-term $PM_{10-2.5}$ exposure and total mortality, which remained positive in copollutant models with $PM_{2.5}$ (Bentayeb et al., 2015), provides the strongest evidence for this relationship. However, there remains a large degree of uncertainty due to the various approaches used to measure $PM_{10-2.5}$ concentrations (see Chapter 3). The lack of information on the spatial and temporal correlation between the various measurement approaches reduces the confidence in the associations observed across studies. Additionally, the evidence from the assessment of long-term $PM_{10-2.5}$ exposures and cardiovascular and respiratory morbidity and metabolic disease provide limited biological plausibility for $PM_{10-2.5}$-related mortality. Although recent studies attempt to address previously identified uncertainties and limitations in the $PM_{10-2.5}$-mortality relationship, the overall assessment of potential copollutant confounding remains limited. **Collectively, this body of evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and total mortality.**

Table 11-12 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Evidence from multiple epidemiologic studies is generally supportive but not entirely consistent	Positive associations from several cohort studies, but not a consistent pattern of associations for total mortality	Table 11-11	Mean concentrations across cities: 4.0–27.3 μg/m^3
Uncertainty regarding epidemiologic evidence from copollutant models to support and independent $PM_{10-2.5}$ association	$PM_{10-2.5}$ effect estimates often attenuated after adjustment for $PM_{2.5}$	Section 11.3.2	
Uncertainty regarding exposure measurement error	Across studies, $PM_{10-2.5}$ concentrations are measured using a number of approaches (i.e., directly measured from dichotomous sampler, difference between PM_{10} and $PM_{2.5}$ concentrations measured at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared in terms of whether they have similar spatial and temporal correlations	Table 11-11 Section 3.3.1.1	
Biological plausibility from studies of cardiovascular morbidity	Expanded body of evidence provides some evidence for associations between long-term $PM_{10-2.5}$ exposure and IHD and stroke	Section 6.5.2 and Section 6.5.5	Mean (across studies): 7.3–31.0 μg/m^3

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal diameter of 2.5 μm.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

11.5 Short-Term UFP Exposure and Total Mortality

The 2009 PM ISA concluded that the "epidemiologic evidence is inadequate to infer a causal relationship between short-term UFP exposure and mortality" (U.S. EPA, 2009). In both the 2004 PM

AQCD and the 2009 PM ISA a few studies examined the association between short-term UFP exposure and mortality with all of the studies being conducted in Europe. Across studies there was inconsistency in the lag structure of associations, which was not consistent with the lag structure observed for other PM size fractions, and the interpretation of the evidence was further complicated by the correlation between UFPs and gaseous copollutants, specifically from combustion sources. Additionally, at the completion of the 2009 PM ISA inherent limitations across all UFP epidemiologic studies was evident and also applicable to the mortality studies. Specifically, it was noted that there is a relatively limited amount of monitoring data within the U.S. that is reflected by no U.S. based studies focusing on short-term UFP exposure and mortality; limited information on the spatial and temporal variability in UFP concentrations; and limited data on the spatial and temporal evolution of UFP size distributions along with data on the composition of UFPs (U.S. EPA, 2009).

Within this ISA, the evaluation of the relationship between short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and mortality focuses on studies that further characterize the relationship, or addresses uncertainties and limitations in the evidence, respectively (Section 11.2.1 and Section 11.3.1). For UFPs, the literature base for all health effects, not just mortality, is much smaller than that for the other PM size fractions. An overall limitation in the health evidence that has complicated the interpretation of results across studies, both those evaluated in the 2009 PM ISA and recent studies that specifically examined associations between short-term UFP exposure and mortality, is the different exposure metrics used (i.e., number concentration [NC], mass concentration [MC], surface area concentration [SC]). As detailed in the Preface, the evaluation of the evidence for UFPs relies on studies that examine MC and SC for particles < 0.3 μm and NC any size range that includes particles <0.1 μm (see Preface).

As detailed in Section 11.1.2, within this section the discussion will focus on the evaluation of multicity studies, but a stronger reliance on large single-city studies due to most UFP and mortality studies to date occurring in individual cities. Additionally, compared to studies that examined short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and mortality, most recent studies of UFPs have not focused on total (nonaccidental) mortality, but instead on cause-specific mortality. As such, cause-specific mortality studies will be discussed in more detail within this section compared to the sections on $PM_{2.5}$ and $PM_{10-2.5}$. The multicity and single-city studies discussed throughout this section, along with study-specific details, air quality characteristics, including size fraction and exposure metric, and the location of UFP monitor(s) is detailed in Table 11-13.

Table 11-13 Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
Breitner et al. (2009) Erfurt, Germany 1991–2002[a] Total	NC (cm^{-3}) 10–100 nm[b]	12,910	---	One monitor 1 km south of city center and 40 m from nearest major road[c]	Correlation (*r*): 0.62 NO_2, 0.51 CO, 0.57 PM_{10}, 0.48 $PM_{2.5}$ Copollutant models examined with: NO_2, CO, PM_{10}, $PM_{2.5}$	% Increase (95% CI) (per 8,439 cm^{-3}) 9/1995–2/1998: 5.5 (1.1, 10.5); lag 0–5 3/1998–3/2002: −1.1 (−6.8, 4.9); lag 0–5
Stölzel et al. (2007) Erfurt, Germany 1995–2001 Total cardio-respiratory	NC (cm^{-3}): 10–30 nm 30–50 nm 50–100 nm 10–100[d] nm	NC 10–30 nm: 9,016 30–50 nm: 2,801 50–100 nm: 1,731 10–100 nm: 13,491	NC: 10–30 nm 75th: 11,574 95th: 21,327 30–50 nm 75th: 3,502 95th: 6,870 50–100 nm 75th: 2,147 95th: 4,202 10–100 nm 75th: 17,030 95th: 31,253	One monitor 1 km south of city center and 40 m from nearest major road	Correlation (*r*)[e]: (Across NC size fractions) 0.60–0.61 NO_2 0.52–0.67 NO 0.50–0.62 CO 0.48–0.74 PM_{10} Copollutant models examined with: NO_2, NO, CO	% Increase (95% CI) (per 9,748 cm^{-3}) Total: 2.9 (0.3, 5.5); lag 4 Cardio-respiratory: 3.1 (0.3, 6.0); lag 4

Table 11-13 (Continued): Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
Kettunen et al. (2007) Helsinki, Finland 1998–2004 Stroke	NC (cm^{-3}) <100 nm	Cold: 8,986[f] Warm: 7,587[f]	Cold: 75th: 13,970 Max: 52,800 Warm: 75th: 11,100 Max: 23,070	1998–2001: One monitor on 20 m high peninsular a few hundred meters from urban areas 3/2001–2004: hilltop 3 km from original site, 4th floor of office building, 100 m from major highway	Correlation (*r*): Cold 0.37 $PM_{2.5}$ 0.33 PM_{10} 0.18 $PM_{10-2.5}$ 0.47 CO −0.10 O_3 0.68 NO_2 Warm 0.30 $PM_{2.5}$ 0.44 PM_{10} 0.47 $PM_{10-2.5}$ 0.39 CO 0.03 O_3 0.61 NO_2 Copollutant models examined with: NR	% Increase (95% CI) (per 4,979 cm^{-3}) 8.5 (−1.2, 19.1); lag 1
†Lanzinger et al. (2016)g Five Central European cities (UFIREG) 2011–2014 Total cardiovascular respiratory	NC (cm^{3-}) 20–100 nm 20–800 nm[h]	20–100 nm: 4,197–5,880 20–800 nm: 5,799–7,775	Max: 20–100 nm: 13,920–28,800 20–800 nm: 16,710–29,470	One urban or suburban back-ground site in each city with no heavy traffic roads in immediate vicinity	Correlation (*r*): 20–100 nm: 0.26–0.54 NO_2 0.29–0.43 PM_{10} 0.40–0.51 $PM_{10-2.5}$ 0.25–0.37 $PM_{2.5}$ 20–800 nm: 0.45–0.62 NO_2 0.54–0.59 PM_{10} 0.45–0.58 $PM_{10-2.5}$ 0.49–0.50 $PM_{2.5}$ Copollutant models examined with: NR	% Increase (95% CI) (20–100 nm: per 2,750 cm^{-3} 20–800 nm: 3,675 cm^{-3}) Total: 20–100 nm 0.1 (−2.0, 2.4); lag 0–1 20–800 nm −0.2 (−2.4, 2.1); lag 0–1 Cardiovascular: 20–100 nm −0.2 (−5.5, 5.4); lag 0–5 20–800 nm −0.1 (−5.5, 5.6); lag 2–5 Respiratory: 20–100 nm 9.9 (−6.3, 28.8); lag 0–5 20–800 nm 5.8 (−6.4, 19.7); lag 2–5

Table 11-13 (Continued): Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
†Stafoggia et al. (2017)[i] Eight European cities 1999–2013[i] Total cardiovascular respiratory	NC (cm^{-3})[j] 4–3,000 nm	5,105–34,046	75th: 6,382–44,208 95th: 9,998–73,044	One urban or suburban background site, except for Rome, which was oriented near traffic sources	Correlation (*r*): 0.13 0.51 PM_{10}, 0.07–0.56 $PM_{2.5}$, 0.09–0.41 $PM_{10-2.5}$, 0.28–0.69 NO_2, 0.07–0.67 CO, −0.52–0.19 O_3 Copollutant models examined with: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, NO_2, CO, O_3	% Increase (95% CI) (per 10,000 cm^{-3}) Total: 0.35 (−0.05, 0.75); lag 6 (Quantitative results not presented for cardiovascular and respiratory mortality.)
†Samoli et al. (2016) London, U.K. 2011–2012 Total cardiovascular respiratory	NC (cm^{-3})[k] Total: <3,000 nm Source specific: <600 nm	Total: 12,123[f] Urban background: 1,893[f] Nucleation: 279[f] Secondary: 104[f] Traffic: 2,355[f]	90th: Total: 17,901 Urban background: 4,442 Nucleation: 991 Secondary: 622 Traffic: 3,950	One urban background site	Correlation (*r*): NR Copollutant models examined with: NR	% Increase (95% CI) (per 5,180 cm^{-3}) <3,000 nm Total: −0.06 (−1.16, 1.06); lag 1 Cardiovascular: −2.04 (−3.94, −0.10); lag 1 Respiratory: −1.86 (−4.50, 0.86); lag 2

Table 11-13 (Continued): Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
†Breitner et al. (2011) Beijing, China 3/2004–8/2005 Cardiovascular ischemic heart disease cerebrovascular	NC (cm^{-3}) <30 nm 30–100 nm <800 nm SC (μm^2 cm^{-3}) 0.1–0.3 µm MC ($\mu g/m^3$) 0.1–0.3 µm	NC[f] <30 nm: 10,430 30–100 nm: 13,260 <800 nm: 33,500 SC[f] 0.1–0.3 µm: 567.0 MC[f] 0.1–0.3 µm: 27.8	NC <30 nm: 75th: 17,120 Max: 61,930 30–100 nm: 75th: 16,380 Max: 31,080 <800 nm: 75th: 40,690 Max: 86,820 SC 0.1–0.3 µm: 75th: 819.6 Max: 2,076.0 MC 0.1–0.3 µm: 75th: 40.2 Max: 105.1	One urban back-ground site a few hundred meters from a major road	Correlation (*r*): NR Copollutant models examined with: NR	% Increase (95% CI) Cardiovascular: NC; lag 0–4 <30 nm (per 7,448 cm^{-3}) 2.13 (−1.80, 6.22) 30–100 nm (per 4,150 cm^{-3}) 2.99 (−0.66, 6.77) <800 nm (per 12,060 cm^{-3}) 4.19 (−0.76, 9.37) SC; lag 0–4 0.1–0.3 µm (per 265.9 μm^2 cm^{-3}) 0.24 (−2.72, 3.29) MC; lag 0–4 0.1–0.3 µm (per 14.0 $\mu g/m^3$) 0.13 (−2.87, 3.23)

Table 11-13 (Continued): Study-specific details and UFP concentrations from studies in the 2009 PM ISA and recent studies.

Study/Location/Years/ Mortality Outcome(s)	UFP Metric/Size Range	Mean	Upper Percentiles	Location of UFP Monitor(s)	Copollutant Examination	Results
†Leitte et al. (2012) Beijing, China 3/2004–8/2005 Respiratory	NC (cm^{-3}) 3–10 nm 10–30 nm 30–50 nm 50–100 nm 3–100 nm 3–1,000 nm	3–10 nm: 4,700 10–30 nm: 8,600 30–50 nm: 5,700 50–100 nm: 7,700 3–100 nm: 27,000 3–1,000 nm: 34,000	95th: 3–10 nm: 11,000 10–30 nm: 14,000 30–50 nm: 8,200 50–100 nm: 11,400 3–100 nm: 39,000 3–1,000 nm: 46,000	One urban background site, 20 m above ground, and 500 m from major road	Correlation (*r*): Across NC size fractions −0.23–0.60 PM_{10}, −0.06–0.51 SO_2, −0.33–0.69 NO_2 Copollutant models examined with: PM_{10}, SO_2, NO_2	% Increase (95% CI); lag 0–4 3–10 nm (per 5,300 cm^{-3}) 4.6 (−5.4, 15.6) 10–30 nm (per 5,300 cm3−) 3.5 (−8.5, 17.1) 30–50 nm (per 2,700 cm^{-3}) −1.7 (−11.7, 9.4) 50–100 nm (per 3,800 cm^{-3}) 1.8 (−8.0, 12.7) 3–100 nm (13,000 cm^{-3}) 3.9 (−7.3, 16.4) 3–1,000 nm (per 14,000 cm^{-3}) 8.9 (−3.8, 16.4)

MC = mass concentration; NC = number concentration; SC = surface area concentration.

[a]Study period 1 October 1991 through 31 March 2002.

[b]Also examined associations with NC 0.01–0.03 µm, 0.03–0.05 µm, and 0.05–0.1 µm.

[c]Particle size distribution measured winter 1991-1992 and 1995 onward, UFP measurements imputed for missing time periods.

[d]Missing data imputed.

[e]Correlations reported only for other NAAQS pollutants.

[f]Median concentration.

[g]PM only measured in four of the five cities.

[h]For one city the range was 0.02–0.5 µm.

[i]Only three cities explicitly measured particles in the ultrafine range (i.e., <100 nm), and each city had to have at least 3 years of continuous data.

[j]NC used as a proxy for UFPs because only three cities explicitly measured UFPs.

[k]Monitor used for total NC had upper size limit of 3 µm while the monitor used for the source apportionment NC collection had an upper size limit of 0.6 µm.

†Studies published since the 2009 PM ISA.

11.5.1 Biological Plausibility for Short-Term UFP Exposure and Total Mortality

The preceding chapters characterized evidence related to evaluating (to the extent possible) the biological plausibility by which short-term UFP exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity (Section 6.5.1 and Section 5.5.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.5.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to UFP could result in cardiovascular effects. Similarly, Section 5.5.1 characterizes the available evidence by which inhalation exposure to UFP could progress from initial events to endpoints relevant to the respiratory system. While there is some evidence for initial events, including injury, inflammation and oxidative stress, the evidence for how these initial events could lead to the subsequent endpoints, and eventually increases in respiratory emergency department (ED) visits and hospital admissions is limited. Collectively, there is limited available evidence for cardiovascular and respiratory morbidity supporting potential biological pathways by which short-term UFP exposures could result in mortality.

11.5.2 Associations Between Short-Term UFP Exposure and Total Mortality in Multicity Studies

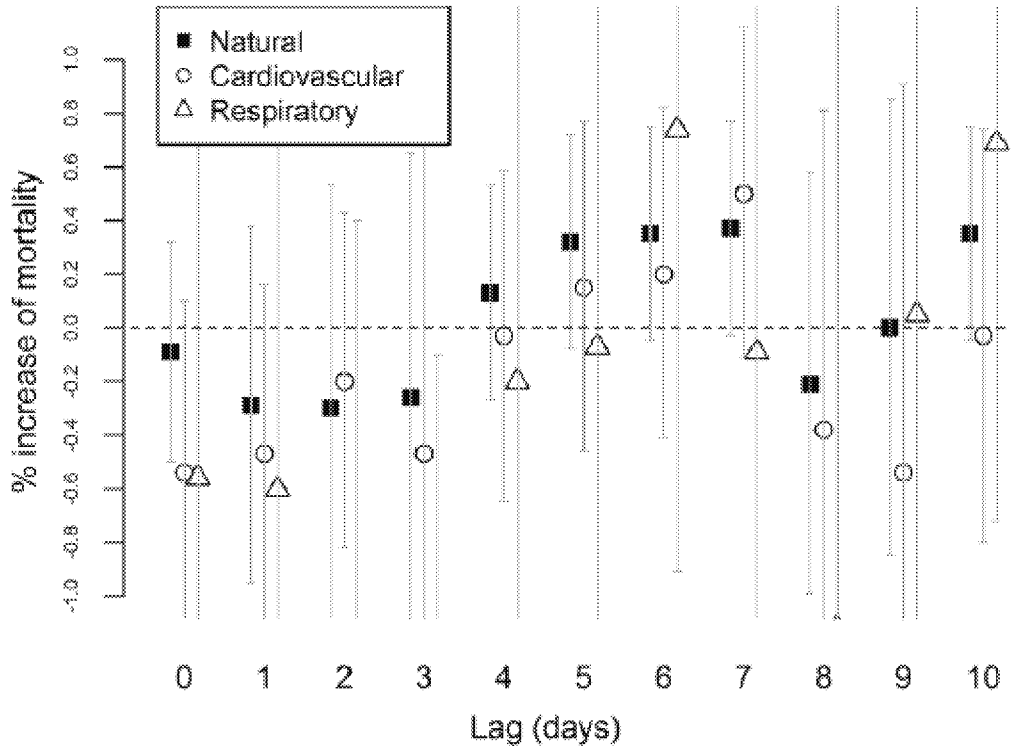
The majority of recent studies examining the association between short-term UFP exposure and mortality have primarily been conducted in individual cities. Lanzinger et al. (2016) and Stafoggia et al. (2017) represent the initial multicity studies that examine the relationship between short-term UFP exposure and mortality. Lanzinger et al. (2016) in the UFIREG project (Ultrafine particles—an evidence based contribution to the development of regional and European environmental and health policy) focused on examining short-term UFP exposure and mortality in five cities in Central and Eastern Europe, but was limited to approximately 2 years of data in each city. Stafoggia et al. (2017) examined short-term UFP exposure and mortality in a study that consisted of eight European cities mostly in Western Europe with at least 3 years of data in each city. Within Lanzinger et al. (2016) the UFP fraction was divided into two distinct metrics, and referred to as UFPs where NC was estimated for sizes ranging from 20 to 100 nm and a NC specific metric that included sizes ranging from 20 to 800 nm with one city having a smaller range of 20 to 500 nm. This approach differed from Stafoggia et al. (2017) where across cities only three explicitly measured particles within the traditional ultrafine range of <100 nm; as a result, NC was used as a proxy for UFPs in each city.

In a time-stratified case-crossover analysis, Lanzinger et al. (2016) examined immediate (lag 0−1), delayed (lag 2−5), and prolonged (lag 0−5) effects of UFP and NC exposure on mortality. Across all of the lags examined for UFP and NC, the authors observed no evidence of an association for total

(nonaccidental) or cardiovascular mortality. Lanzinger et al. (2016) reported a positive, but imprecise, association with respiratory mortality for UFP and NC across all lags with the association largest in magnitude for UFP at lag 0–5 (9.9% [95% CI: −6.3, 28.8] per 2,750 $cm^{-3}$and NC at lag 2–5 (5.8% [95% CI: −6.4, 19.7] per 3,675 cm^{-3}). No evidence of an association was observed with respiratory mortality and the other PM size fractions examined. Although some sensitivity analyses focusing on model specification were conducted based on the UFP—respiratory mortality association, the wide confidence intervals complicate the interpretation of these analyses.

While Lanzinger et al. (2016) focused on examining the lag structure of associations across different multiday lags, Stafoggia et al. (2017) focused on examining whether there was evidence of an association between short-term UFP exposure and mortality across a range of single-day lags (i.e., 0 to 10 days). Across the single-lag days examined, the authors reported evidence of positive associations with total (nonaccidental) mortality at lags 5 through 7 ranging from 0.32–0.37%, with associations largest in magnitude for respiratory (lag 6) and cardiovascular (lag 7) mortality also within this range, although there were wide confidence intervals (Figure 11-30). Subsequent copollutant and sensitivity analyses focused specifically on associations reported for lag 6, where single-pollutant models resulted in a 0.35% increase in total (nonaccidental) mortality (95% CI: −0.05, 0.75) for a 10,000 particle/cm^3 increase in 24-hour average NC.

The results from copollutant analyses indicate that associations with total (nonaccidental) mortality are relatively unchanged in models with CO (0.30%) and O_3 (0.27%), while there was some evidence of an attenuation in models with PM_{10} (0.22%). The authors reported no evidence of an association with NC in copollutant models with $PM_{2.5}$, $PM_{10-2.5}$, and NO_2, providing some evidence of potential confounding. Complicating the overall interpretation of results from Stafoggia et al. (2017) is that further analysis of the pooled results across cities identified that the positive association observed at lag 6 was largely driven by the city of Rome. As a result, when excluding Rome from the meta-analysis there was no evidence of an association between short-term NC exposure and total (nonaccidental) mortality.



Note: Natural = total (nonaccidental) mortality.
Source: Permission pending, Stafoggia et al. (2017).

Figure 11-30 Percent increase in total (nonaccidental), cardiovascular, and respiratory mortality across eight European cities for a 10,000 particle/cm^3 increase in 24-hour average number concentration (NC) across lags 0 to 10 days.

11.5.3 Associations Between Short-Term UFP Exposure and Total Mortality in Single-City Studies

Recent single-city studies all examined a number of different size fractions of particles within the ultrafine range along with exposure metrics, as detailed in Table 11-13. In many cases the size fractions examined are a reflection of the monitor used. For example, some monitors that measure NC result in a larger size distribution being measured than others (Section 2.4.3). As a result, the NC metric is considered a proxy for UFP exposure due to the potential for particles larger than the traditional 100 nm cutoff for UFPs being included in the measurement (Section 2.4.3.1). Overall, the inconsistency in the size fractions examined across studies complicates the interpretation of results, but collectively can inform if there is evidence of a relationship between short-term UFP exposure and mortality.

The single-city studies conducted to date that examined short-term UFP exposure and mortality are limited to Europe and Asia. Samoli et al. (2016) in a study conducted in London, U.K. used a

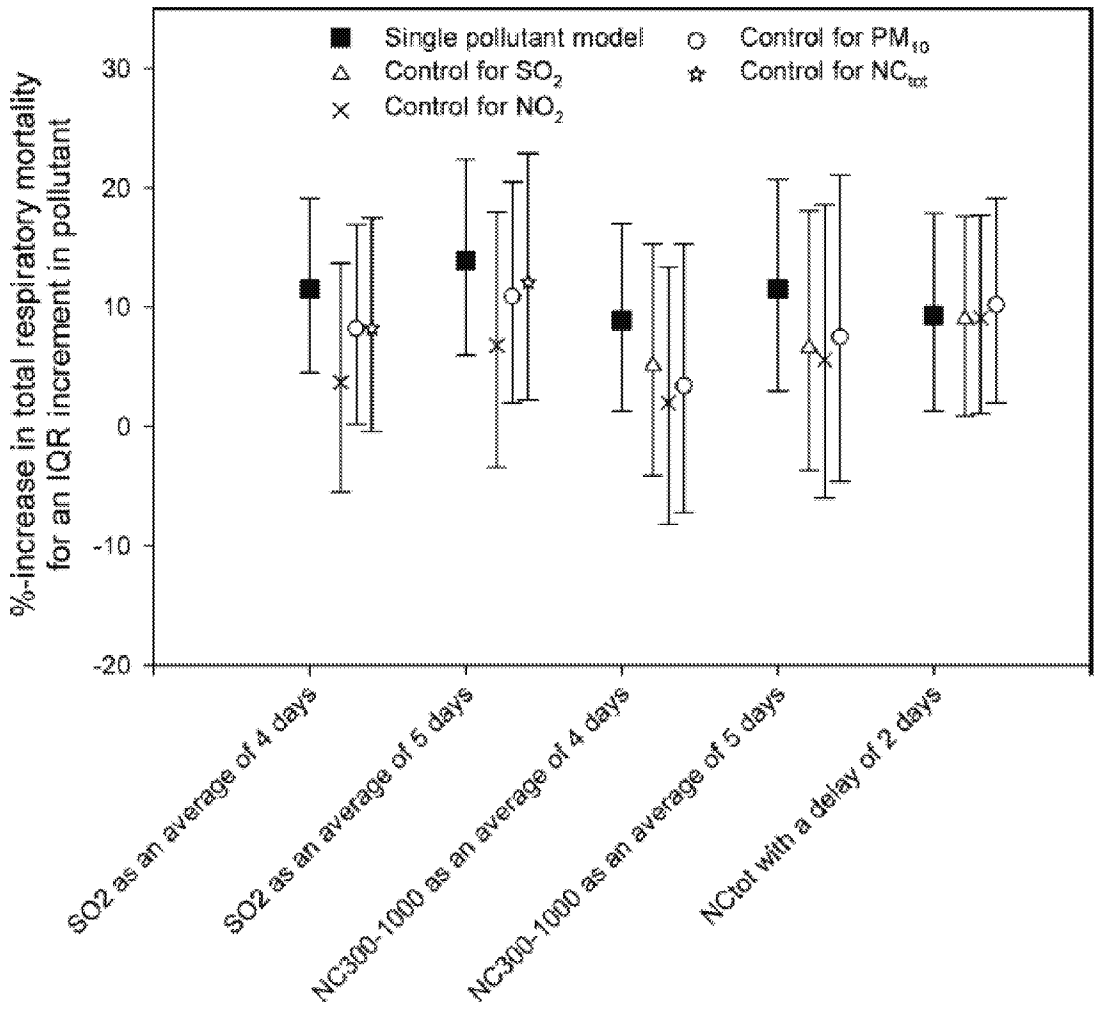
traditional source apportionment method (i.e., positive matrix factorization) to identify UFP sources based on NC data. The source apportionment analyses identified four sources each with a different peak in the size distribution: urban background (30 nm), nucleation (70 nm), secondary (20 nm), and traffic (250 nm). In analyses focusing on total (nonaccidental) and cardiovascular mortality at lag 1 and respiratory mortality at lag 2, the authors reported no evidence of an association with total NC. When examining source-specific NC, a small positive association was observed for total (nonaccidental) mortality and nucleation and traffic sources (~0.20% increase), but confidence intervals are wide. There was no evidence of an association with any NC sources and cardiovascular mortality with evidence of a positive association between respiratory mortality and only the urban background source (1.4% increase [95% CI: −0.97, 3.89] for a 1,806 number/cm^3 increase). When measuring NC, although a large percentage of particles are <0.1 μm (see Section 2.4.3.1), the authors used two different types of monitors with different size ranges for the NC and source-specific NC analysis, resulting in some degree of uncertainty when comparing the NC and source-specific NC results.

The single-city studies conducted in China systematically examined various UFP size fractions and exposure metrics. Breitner et al. (2011) and Leitte et al. (2012) were both conducted in Beijing, China over the same study duration, but focused on different UFP size fractions and metrics as well as mortality outcomes. Both Breitner et al. (2011) and Leitte et al. (2012) examined some particle size ranges that are outside the scope of the UFP - mortality evaluation and are detailed in Section 11.1.9. Breitner et al. (2011) in a study focusing on cardiovascular-related mortality, in addition to focusing on NC, converted NC to SC, assuming spherical particles with constant density, and MC, assuming a density of 1.5 g/cm^3. For cardiovascular mortality, the authors observed positive associations, but with wide confidence intervals for all NC metrics at lag 0-4 days (see Table 11-13). Positive, but uncertain, associations were also observed for $SC_{0.1\text{-}0.3}$ and $MC_{0.1\text{-}0.3}$ at lag 0−4 days ($SC_{0.1-0.3}$: 0.24% [95% CI: −2.72, 3.29] per IQR [265.9 μm^2cm^{3-}]; $MC_{0.1-0.3}$: 0.13% [95% CI: −2.87, 3.23] per IQR [14.0 μg/m^3]). When comparing the multiday lag results to single-day lags, there was variability in the magnitude and direction of the association across single-day lags across metrics, while the multiday average lag was consistently positive. A similar pattern of associations was observed for ischemic heart disease mortality. Copollutant models focused only on the Aitken mode particles and NC_1 at lag 2. Across the copollutant models, when including the other size fractions examined in the model ranging up to 1 μm, both Aitken mode particles (0.03−0.1 μm) and NC1 (<0.8 μm) associations were robust. Breitner et al. (2011) also examined whether the UFP associations were modified by specific types of air masses identified through cluster analysis. The authors did not observe any evidence that air mass origin modified NC associations, however, mortality associations at lag 2 for the SC and MC metrics were stronger for air masses representative of stagnant air masses and air masses originating from Southern China.

Unlike Breitner et al. (2011), Leitte et al. (2012) only focused on NC metrics and respiratory mortality. Across the different UFP size fractions, the authors reported consistent positive associations between respiratory mortality and NC for all particle fractions between 3 nm and 1 μm at lag 2, but confidence intervals were wide. Focusing on lag 0−3 days, the strongest association was observed for

NC_{total}, which was defined as particles ranging in size from 3 nm–1 μm where Leitte et al. (2012) reported an 8.9% (95%CI: −3.8, 23.3%) increase in respiratory mortality per IQR increase (14,000 cm^{3-}). In comparison, for UFP, which was defined as particles ranging in size from 3–100 nm, the authors observed a 3.9% (95%CI: −7.3, 16.4%) increase per IQR increase (13,000 cm^{3-}). When comparing the results from single-day lags to multiday averages (i.e., 0–4 and 0–5 days), the magnitude of the association between all of the size fractions, except the 30–50 nm size fraction, and respiratory mortality were larger in magnitude, but the confidence intervals were also larger compared to the single-day lag estimates. Whereas Breitner et al. (2011) only focused on copollutant models with other UFP size fractions, Leitte et al. (2012) examined gaseous pollutants, for NC_{total} and found associations remained relatively unchanged in models with NO_2 and SO_2 (Figure 11-31).

Leitte et al. (2012) also examined potential modification of the respiratory mortality and UFP relationship by different air masses, focusing on the NC_{total} fraction, and similar to the cardiovascular mortality results in Breitner et al. (2011) observed some evidence that particularly stagnant air masses as well as air masses originating from some areas of China may modify the NC_{total} association.



Source: Permission pending, Leitte et al. (2012).

Figure 11-31 Association between short-term number concentration (NC)300−1,000 and NC_{total} exposure in single and copollutant models and respiratory mortality in Beijing, China.

11.5.4 Summary and Causality Determination

Compared to the examination of other PM size fractions, a smaller number of studies have examined the association between short-term UFP exposure and total (nonaccidental) mortality. At the completion of the 2009 PM ISA, the overall body of evidence was limited and based on a few single-city studies that provided some evidence of positive associations, but at lags longer than those observed for other PM size fractions. Recent evidence from both multi- and single-city studies provides additional insight on the relationship between short-term UFP exposure and mortality, but the uncertainties and limitations in the evidence identified in the 2009 PM ISA remain, including, but not limited to: the metric

to examine UFP exposures (i.e., NC, SC, or MC); the size range to consider when examining UFP exposures; exposure measurement error due to the spatial and temporal variability in UFPs; and the correlation between UFPs and gaseous pollutants, which collectively continue to support that the evidence is inadequate to infer a causal relationship. Although there is evidence of positive associations for NC for different size fractions in a few studies, confidence intervals are often wide, and studies did not monitor and, subsequently examine, the same UFP size fractions complicating the interpretation of results across studies. Additionally, there is limited and inconsistent cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity evidence to provide biological plausibility to support the positive associations observed in some studies for total mortality. This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for short-term exposures to UFPs using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-14.

Recent multi- and single-city studies that examined the association between short-term UFP exposure and total (nonaccidental) mortality provide inconsistent evidence of a positive association, which is further supported by studies that examined cardiovascular and respiratory mortality. The evaluation of the evidence from recent studies is complicated by the different UFP size fractions examined and exposure metrics used (i.e., NC, SC, and MC). Across studies, the majority primarily examined UFP associations using the NC metric, but the range of size fractions examined varied preventing a complete comparison of the pattern of associations across studies. Of the few studies that examined copollutant confounding, the focus was on examining associations with NC. In the assessment of copollutant confounding, the NC size fractions examined varied from focusing on a specific size fraction range (e.g., 0.03−0.1 μm) to total NC. The copollutant model results provided evidence that the NC associations were both robust and sensitive to adjustment depending on the PM size fraction and gaseous pollutant included in the model.

Across epidemiologic studies that examined short-term UFP exposure and mortality, an inherent limitation is the use of primarily one monitoring site to estimate exposure, which potentially contributes to exposure measurement error. The potential for exposure measurement error is reflected in the limited number of studies demonstrating greater spatial variability in UFP concentrations (i.e., NC) as well as changes in the particle size distribution at increasing distances from sources (Section 2.5.1.1.5, Section 2.5.1.2.4, Section 3.4.5) There is also limited information on the temporal variability in UFP concentrations (i.e., NC) over an urban area (Section 2.5.2.2.3).

Table 11-14 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between short-term UFP exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Inconsistent epidemiologic evidence from a limited number of studies at relevant UFP concentrations	Some evidence of positive, but imprecise, increases in mortality in multicity and single-city studies conducted in Europe and Asia, with no studies conducted in the U.S. Limited evidence of positive associations for cardiovascular and respiratory mortality in multi- and single-city studies conducted in Europe, and Asia, with no studies conducted in the U.S.	Section 11.5.2 Section 11.5.3 Table 11-13 Section 5.5.8 Section 6.5.8	24−h avg: NC: Variability in UFP size ranges examined prevents providing a range. SC (μm^2 cm^{-3}) 0.1–0.3 µm: 567.0 MC ($\mu g/m^3$) 0.1–0.3 µm: 27.8
Limited epidemiologic evidence from copollutant models for an independent UFP association	Some evidence that UFP associations using the NC metric are relatively unchanged with CO and O_3 and other NC size ranges, but potentially attenuated with $PM_{2.5}$, $PM_{10-2.5}$, and NO_2.	Section 11.5.2 Section 11.5.3	
Uncertainty regarding exposure metric and UFP size fraction	Inconsistency in the UFP metric used (i.e., NC, SC, and MC) and UFP size fraction examined complicating interpretation of results across studies.	Section 11.4.1	
Uncertainty regarding exposure measurement error	All studies relied on one monitor to measure UFPs, which is inadequate based on limited data demonstrating both that there is greater spatial variability in UFPs (i.e., NC) and that the particle size distribution changes with distance from source. Additionally, there is limited information on the temporal variability in UFP concentrations.	Section 2.5.1.1.5 Section 2.5.1.2.4 Section 2.5.2.2.3 Section 3.4.5 Table 11-13	
Limited and inconsistent evidence for biological plausibility from cardiovascular and respiratory morbidity	Limited evidence from studies examining short-term UFP exposure and respiratory and cardiovascular effects provide limited biological plausibility for a relationship between short-term UFP exposure and cardiovascular- and respiratory-related mortality.	Section 5.5 Section 6.7	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015b).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

Overall, recent epidemiologic studies that examined short-term UFP exposure and mortality provide limited and inconsistent evidence of a positive association in both single and copollutant models. There is also limited evidence of biological plausibility from the assessment of short-term UFP exposures and respiratory and cardiovascular morbidity to support potential UFP-related mortality (Section 5.5, Section 6.7). Additionally, across studies there is a lack of consistency in terms of the UFP metric and size fractions examined, which complicate the interpretation of results, along with the potential for exposure measurement error due to uncertainty in the spatial and temporal variability in UFP concentrations. **Collectively, the epidemiologic evidence is inadequate to infer the presence or absence of a causal relationship between short-term UFP exposure and total mortality.**

11.6 Long-Term UFP Exposure and Total Mortality

The 2009 PM ISA reported that no epidemiologic studies evaluated the effects of long-term UFP exposure and mortality, concluding that the evidence was "inadequate to determine if a causal relationship exists between long-term UFP exposure and mortality." A recent study provides some additional evidence to inform the relationship between long-term UFP exposure and mortality, though the overall evidence base remains limited.

11.6.1 Biological Plausibility for Long-Term UFP Exposure and Total Mortality

The preceding chapters characterized evidence related to evaluating the biological plausibility by which long-term UFP exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity (Section 6.6.1 and Section 5.6.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.6.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to UFPs could result in initial events to endpoints relevant to the cardiovascular system. Similarly, Section 5.6.1 characterizes the available evidence by which inhalation exposure to UFPs could progress from initial events to endpoints relevant to the respiratory system. This evidence is limited to several experimental studies of oxidative stress and inflammatory changes that do not provide consistent evidence for initial events or progression along a plausible pathway from UFP exposure to respiratory health endpoints. Collectively, there is limited available evidence for cardiovascular and respiratory morbidity supporting potential biological pathways by which long-term UFP exposures could result in mortality.

11.6.2 Associations between Long-Term UFP Exposure and Total Mortality

In 2009, Hoek et al. (2009) published an expert elicitation in which 11 European experts in epidemiology, toxicology and clinical science were asked to quantify the relationship between UFP exposure and health endpoints, including mortality. The experts emphasized that the lack of studies examining long-term UFP exposure and mortality contributed greatly to the uncertainty of this relationship. The experts were asked to estimate the "percent change in annual, total (nonaccidental) mortality in the general EU [European Union] population resulting from a permanent 1,000 particles/cm^2 reduction in annual average UFP across Europe (given a population-weighted baseline concentration of 20,000 particles/cm^2)." While there was substantial variability, the median response from the experts was a 0.30% decrease in annual, total (nonaccidental) mortality, though none of the experts excluded the possibility that UFPs had no effect. In a recent study, Ostro et al. (2015) examined the association between UFP (<0.1 μm) mass concentrations and mortality among women in the California Teachers Cohort. The authors used a chemical transport model to predict UFP concentrations with a 4-km spatial resolution, observing a positive association with IHD mortality (HR: 1.10; 95% CI: 1.02, 1.18, per 0.969 μg/m^3 increase). Associations with total (nonaccidental), cardiovascular, and respiratory mortality were near the null value.

Overall, the literature base for long-term UFP exposure and mortality remains very small, with one study (Ostro et al., 2015) reporting results for UFP mass concentration. There are no studies that examine UFP number concentration. An expert elicitation conducted in Europe (Hoek et al., 2009) asked experts in epidemiology, toxicology and clinical sciences to review the available evidence for the health effects of UFPs. The experts concluded that long-term exposure could affect mortality risk, but due to the small literature base and associated uncertainties, they could not rule out the possibility of no UFP effect on mortality.

11.6.3 Summary and Causality Determination

This section describes the evaluation of evidence for total (nonaccidental) mortality, with respect to the causality determination for long-term exposures to UFPs using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-15. Compared to the examination of other PM size fractions, a smaller number of studies have examined the association between long-term UFP exposure and total (nonaccidental) mortality. At the completion of the 2009 PM ISA, there were no available studies examining long-term UFP exposure and total mortality. Recent evidence from the CA Teachers cohort provides little insight on the relationship between long-term UFP exposure and mortality due to generally null associations and the uncertainties and limitations in the evidence base. Additionally, there is limited and inconsistent cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity evidence to provide biological

plausibility to support an association between UFPs and total mortality. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and total mortality.**

Table 11-15 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited and inconsistent epidemiologic evidence	Single study observes generally null association with total mortality	Ostro et al. (2015)	1,293 ng/m^3
Uncertainty regarding potential confounding by copollutants	No studies examine potential confounding of UFP associations by copollutants	Section 11.6.2	
Uncertainty regarding exposure measurement error	Chemical transport model to predict UFP concentrations with a 4-km spatial resolution	Ostro et al. (2015)	
Uncertainty regarding biological plausibility	Little evidence for long-term UFP exposure and cardiovascular or respiratory morbidity	Section 5.6 and Section 6.7	

UFP = ultrafine particle.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the UFP concentrations with which the evidence is substantiated.

11.7 References

Adar, SD; Filigrana, PA; Clements, N; Peel, JL. (2014). Ambient coarse particulate matter and human health: A systematic review and meta-analysis [Review]. Curr Environ Health Rep 1: 258-274. http://dx.doi.org/10.1007/s40572-014-0022-z

American Heart Association. (2011). Cardiovascular disease statistics. Available online at http://web.archive.org/web/20110410093532/http://www.americanheart.org/presenter.jhtml?identifier=4478 (accessed April 12, 2011).

Atkinson, RW; Kang, S; Anderson, HR; Mills, IC; Walton, HA. (2014). Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis [Review]. Thorax 69: 660-665. http://dx.doi.org/10.1136/thoraxjnl-2013-204492

Austin, E; Coull, B; Thomas, D; Koutrakis, P. (2012). A framework for identifying distinct multipollutant profiles in air pollution data. Environ Int 45: 112-121. http://dx.doi.org/10.1016/j.envint.2012.04.003

Baccarelli, AA; Hales, N; Burnett, RT; Jerrett, M; Mix, C; Dockery, DW; Pope, CA. (2016). Particulate air pollution, exceptional aging, and rates of centenarians: a nationwide analysis of the United States, 1980-2010. Environ Health Perspect 124: 1744-1750. http://dx.doi.org/10.1289/EHP197

Basagaña, X; Jacquemin, B; Karanasiou, A; Ostro, B; Querol, X; Agis, D; Alessandrini, E; Alguacil, J; Artiñano, B; Catrambone, M; de La Rosa, JD; Díaz, J; Faustini, A; Ferrari, S; Forastiere, F; Katsouyanni, K; Linares, C; Perrino, C; Ranzi, A; Ricciardelli, I; Samoli, E; Zauli-Sajani, S; Sunyer, J; Stafoggia, M. (2015). Short-term effects of particulate matter constituents on daily hospitalizations and mortality in five South-European cities: Results from the MED-PARTICLES project. Environ Int 75: 151-158. http://dx.doi.org/10.1016/j.envint.2014.11.011

Baxter, LK; Crooks, JL; Sacks, JD. (2017). Influence of exposure differences on city-to-city heterogeneity in PM2.5-mortality associations in US cities. Environ Health 16: 1. http://dx.doi.org/10.1186/s12940-016-0208-y

Baxter, LK; Duvall, RM; Sacks, J. (2013). Examining the effects of air pollution composition on within region differences in PM(2.5) mortality risk estimates. J Expo Sci Environ Epidemiol 23: 457-465. http://dx.doi.org/10.1038/jes.2012.114

Baxter, LK; Sacks, JD. (2014). Clustering cities with similar fine particulate matter exposure characteristics based on residential infiltration and in-vehicle commuting factors. Sci Total Environ 470-471: 631-638. http://dx.doi.org/10.1016/j.scitotenv.2013.10.019

Beckerman, BS; Jerrett, M; Serre, M; Martin, RV; Lee, S; van Donkelaar, A; Ross, Z, ev; Su, J; Burnett, RT. (2013). A hybrid approach to estimating national scale spatiotemporal variability of PM2.5 in the contiguous United States. Environ Sci Technol 47: 7233-7241. http://dx.doi.org/10.1021/es400039u

Beelen, R; Hoek, G; Houthuijs, D; van den Brandt, PA; Goldbohm, RA; Fischer, P; Schouten, LJ; Armstrong, B; Brunekreef, B. (2009). The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study. Occup Environ Med 66: 243-250. http://dx.doi.org/10.1136/oem.2008.042358

Beelen, R; Raaschou-Nielsen, O; Stafoggia, M; Andersen, ZJ; Weinmayr, G; Hoffmann, B; Wolf, K; Samoli, E; Fischer, P; Nieuwenhuijsen, M; Vineis, P; Xun, WW; Katsouyanni, K; Dimakopoulou, K; Oudin, A; Forsberg, B; Modig, L; Havulinna, AS; Lanki, T; Turunen, A; Oftedal, B; Nystad, W; Nafstad, P; De Faire, U; Pedersen, NL; Ostenson, CG; Fratiglioni, L; Penell, J; Korek, M; Pershagen, G; Eriksen, KT; Overvad, K; Ellermann, T; Eeftens, M; Peeters, PH; Meliefste, K; Wang, M; Bueno-De-Mesquita, B; Sugiri, D; Krämer, U; Heinrich, J; de Hoogh, K; Key, T; Peters, A; Hampel, R; Concin, H; Nagel, G; Ineichen, A; Schaffner, E; Probst-Hensch, N; Künzli, N; Schindler, C; Schikowski, T; Adam, M; Phuleria, H; Vilier, A; Clavel-Chapelon, F; Declercq, C; Grioni, S; Krogh, V; Tsai, MY; Ricceri, F; Sacerdote, C; Galassi, C; Migliore, E; Ranzi, A; Cesaroni, G; Badaloni, C; Forastiere, F; Tamayo, I; Amiano, P; Dorronsoro, M; Katsoulis, M; Trichopoulou, A; Brunekreef, B; Hoek, G. (2014a). Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383: 785-795. http://dx.doi.org/10.1016/S0140-6736(13)62158-3

Beelen, R; Stafoggia, M; Raaschou-Nielsen, O; Andersen, ZJ; Xun, WW; Katsouyanni, K; Dimakopoulou, K; Brunekreef, B; Weinmayr, G; Hoffmann, B; Wolf, K; Samoli, E; Houthuijs, D; Nieuwenhuijsen, M; Oudin, A; Forsberg, B; Olsson, D; Salomaa, V; Lanki, T; Yli-Tuomi, T; Oftedal, B; Aamodt, G; Nafstad, P; De Faire, U; Pedersen, NL; Ostenson, CG; Fratiglioni, L; Penell, J; Korek, M; Pyko, A; Eriksen, KT; Tjønneland, A; Becker, T; Eeftens, M; Bots, M; Meliefste, K; Wang, M; Bueno-De-Mesquita, B; Sugiri, D; Krämer, U; Heinrich, J; de Hoogh, K; Key, T; Peters, A; Cyrys, J; Concin, H; Nagel, G; Ineichen, A; Schaffner, E; Probst-Hensch, N; Dratva, J; Ducret-Stich, R; Vilier, A; Clavel-Chapelon, F; Stempfelet, M; Grioni, S; Krogh, V; Tsai, MY; Marcon, A; Ricceri, F; Sacerdote, C; Galassi, C; Migliore, E; Ranzi, A; Cesaroni, G; Badaloni, C; Forastiere, F; Tamayo, I; Amiano, P; Dorronsoro, M; Katsoulis, M; Trichopoulou, A; Vineis, P; Hoek, G. (2014b). Long-term exposure to air pollution and cardiovascular mortality: An analysis of 22 European cohorts. Epidemiology 25: 368-378. http://dx.doi.org/10.1097/EDE.0000000000000076

Beevers, SD; Kitwiroon, N; Williams, ML; Kelly, FJ; Ross Anderson, H; Carslaw, DC. (2013). Air pollution dispersion models for human exposure predictions in London. J Expo Sci Environ Epidemiol 23: 647-653. http://dx.doi.org/10.1038/jes.2013.6

Bentayeb, M; Wagner, V; Stempfelet, M; Zins, M; Goldberg, M; Pascal, M; Larrieu, S; Beaudeau, P; Cassadou, S; Eilstein, D; Filleul, L; Le Tertre, A; Medina, S; Pascal, L; Prouvost, H; Quénel, P; Zeghnoun, A; Lefranc, A. (2015). Association between long-term exposure to air pollution and mortality in France: A 25-year follow-up study. Environ Int 85: 5-14. http://dx.doi.org/10.1016/j.envint.2015.08.006

Breitner, S; Liu, L; Cyrys, J; Brüske, I; Franck, U; Schlink, U; Leitte, AM; Herbarth, O; Wiedensohler, A; Wehner, B; Hu, M; Pan, XC; Wichmann, HE; Peters, A. (2011). Sub-micrometer particulate air pollution and cardiovascular mortality in Beijing, China. Sci Total Environ 409: 5196-5204. http://dx.doi.org/10.1016/j.scitotenv.2011.08.023

Breitner, S; Stölzel, M; Cyrys, J; Pitz, M; Wölke, G; Kreyling, W; Küchenhoff, H; Heinrich, J; Wichmann, H; Peters, A. (2009). Short-term mortality rates during a decade of improved air quality in Erfurt, Germany. Environ Health Perspect 117: 448-454. http://dx.doi.org/10.1289/ehp.11711

Brook, RD; Cakmak, S; Turner, MC; Brook, J. R.; Crouse, D; Peters, PA; van Donkelaar, A; Villeneuve, PJ; Brion, O; Jerrett, M; Martin, RV; Rajagopalan, S; Goldberg, MS; Pope, CA, III; Burnett, RT. (2013). Long-Term Fine Particulate Matter Exposure and Mortality From Diabetes in Canada. Diabetes Care 36: 3313-3320. http://dx.doi.org/10.2337/dc12-2189

Burnett, RT; Goldberg, MS. (2003). Size-fractionated particulate mass and daily mortality in eight Canadian cities. Boston, MA: Health Effects Institute.

Burnett, RT; Stieb, D; Brook, JR; Cakmak, S; Dales, R; Raizenne, M; Vincent, R; Dann, T. (2004). Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. Arch Environ Occup Health 59: 228-236. http://dx.doi.org/10.3200/AEOH.59.5.228-236

Carey, IM; Atkinson, RW; Kent, AJ; van Staa, T; Cook, DG; Anderson, HR. (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med 187: 1226-1233. http://dx.doi.org/10.1164/rccm.201210-1758OC

Cesaroni, G; Badaloni, C; Gariazzo, C; Stafoggia, M; Sozzi, R; Davoli, M; Forastiere, F. (2013). Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ Health Perspect 121: 324-331. http://dx.doi.org/10.1289/ehp.1205862

Chen, H; Burnett, RT; Copes, R; Kwong, JC; Villeneuve, PJ; Goldberg, MS; Brook, RD; van Donkelaar, A; Jerrett, M; Martin, RV; Brook, JR; Kopp, A; Tu, JV. (2016). Ambient fine particulate matter and mortality among survivors of myocardial infarction: population-based cohort study. Environ Health Perspect 124: 1421-1428. http://dx.doi.org/10.1289/EHP185

Chen, LH; Knutsen, SF; Shavlik, D; Beeson, WL; Petersen, F; Ghamsary, M; Abbey, D. (2005). The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk? Environ Health Perspect 113: 1723-1729. http://dx.doi.org/10.1289/ehp.8190

Chen, R; Li, Y; Ma, Y; Pan, G; Zeng, G; Xu, X; Chen, B; Kan, H. (2011). Coarse particles and mortality in three Chinese cities: the China Air Pollution and Health Effects Study (CAPES). Sci Total Environ 409: 4934-4938. http://dx.doi.org/10.1016/j.scitotenv.2011.08.058

Chi, GC; Hajat, A; Bird, CE; Cullen, MR; Griffin, BA; Miller, KA; Shih, RA; Stefanick, ML; Vedal, S; Whitsel, EA; Kaufman, JD. (2016). Individual and neighborhood socioeconomic status and the association between air pollution and cardiovascular disease. Environ Health Perspect 124: 1840-1847. http://dx.doi.org/10.1289/EHP199

Correia, AW; Pope, CA, III; Dockery, DW; Wang, Y, un; Ezzati, M; Dominici, F. (2013). Effect of air pollution control on life expectancy in the United States: an analysis of 545 U.S. counties for the period from 2000 to 2007. Epidemiology 24: 23-31. http://dx.doi.org/10.1097/EDE.0b013e3182770237

Cox, LA, (, J.,r; Popken, DA. (2015). Has reducing fine particulate matter and ozone caused reduced mortality rates in the United States? Ann Epidemiol 25: 162-173. http://dx.doi.org/10.1016/j.annepidem.2014.11.006

Crouse, D; Philip, S; van Donkelaar, A; Martin, RV; Jessiman, B; Peters, PA; Weichenthal, S; Brook, J. R.; Hubbell, B; Burnett, RT. (2016). A new method to jointly estimate the mortality risk of long-term exposure to fine particulate matter and its components. Sci Rep 6: 18916. http://dx.doi.org/10.1038/srep18916

Crouse, DL; Peters, PA; Hystad, P; Brook, JR; van Donkelaar, A; Martin, RV; Villeneuve, PJ; Jerrett, M; Goldberg, MS; Pope, CA; Brauer, M; Brook, RD; Robichaud, A; Menard, R; Burnett, RT. (2015). Ambient PM 2.5, O 3, and NO 2 exposures and associations with mortality over 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect 123: 1180-1186. http://dx.doi.org/10.1289/ehp.1409276

Crouse, DL; Peters, PA; van Donkelaar, A; Goldberg, MS; Villeneuve, PJ; Brion, O; Khan, S; Atari, DO; Jerrett, M; Pope, CA; Brauer, M; Brook, JR; Martin, RV; Stieb, D; Burnett, RT. (2012). Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. Environ Health Perspect 120: 708-714. http://dx.doi.org/10.1289/ehp.1104049

Dai, L; Zanobetti, A; Koutrakis, P; Schwartz, JD. (2014). Associations of fine particulate matter species with mortality in the United States: a multicity time-series analysis. Environ Health Perspect 122: 837-842. http://dx.doi.org/10.1289/ehp.1307568

Davis, JA; Meng, Q; Sacks, JD; Dutton, SJ; Wilson, WE; Pinto, JP. (2011). Regional variations in particulate matter composition and the ability of monitoring data to represent population exposures. Sci Total Environ 409: 5129-5135. http://dx.doi.org/10.1016/j.scitotenv.2011.08.013

de Keijzer, C; Agis, D; Ambrós, A; Arévalo, G; Baldasano, JM; Bande, S; Barrera-Gómez, J; Benach, J; Cirach, M; Dadvand, P; Ghigo, S; Martinez-Solanas, È; Nieuwenhuijsen, M; Cadum, E; Basagaña, X; group, M-HS. (2016). The association of air pollution and greenness with mortality and life expectancy in Spain: A small-area study. Environ Int 99: 170-176. http://dx.doi.org/10.1016/j.envint.2016.11.009

Dehbi, HM; Blangiardo, M; Gulliver, J; Fecht, D; de Hoogh, K; Al-Kanaani, Z; Tillin, T; Hardy, R; Chaturvedi, N; Hansell, AL. (2016). Air pollution and cardiovascular mortality with over 25years follow-up: A combined analysis of two British cohorts. Environ Int 99: 275-281. http://dx.doi.org/10.1016/j.envint.2016.12.004

Di, Q; Dai, L; Wang, Y; Zanobetti, A; Choirat, C; Schwartz, JD; Dominici, F. (2017a). Association of short-term exposure to air pollution with mortality in older adults. JAMA 318: 2446-2456. http://dx.doi.org/10.1001/jama.2017.17923

Di, Q; Kloog, I; Koutrakis, P; Lyapustin, A; Wang, Y; Schwartz, J. (2016). Assessing PM2.5 exposures with high spatiotemporal resolution across the Continental United States. Environ Sci Technol 50: 4712-4721. http://dx.doi.org/10.1021/acs.est.5b06121

Di, Q; Rowland, S; Koutrakis, P; Schwartz, J. (2017b). A hybrid model for spatially and temporally resolved ozone exposures in the continental United States. J Air Waste Manag Assoc 67: 39-52. http://dx.doi.org/10.1080/10962247.2016.1200159

Di, Q; Wang, Y; Zanobetti, A; Wang, Y; Koutrakis, P; Choirat, C; Dominici, F; Schwartz, JD. (2017c). Air pollution and mortality in the Medicare population. N Engl J Med 376: 2513-2522. http://dx.doi.org/10.1056/NEJMoa1702747

Dimakopoulou, K; Samoli, E; Beelen, R; Stafoggia, M; Andersen, ZJ; Hoffmann, B; Fischer, P; Nieuwenhuijsen, M; Vineis, P; Xun, W; Hoek, G; Raaschou-Nielsen, O; Oudin, A; Forsberg, B; Modig, L; Jousilahti, P; Lanki, T; Turunen, A; Oftedal, B; Nafstad, P; Schwarze, PE; Penell, J; Fratiglioni, L; Andersson, N; Pedersen, N; Korek, M; De Faire, U; Eriksen, KT; Tjønneland, A; Becker, T; Wang, M; Bueno-De-Mesquita, B; Tsai, MY; Eeftens, M; Peeters, PH; Meliefste, K; Marcon, A; Krämer, U; Kuhlbusch, TA; Vossoughi, M; Key, T; de Hoogh, K; Hampel, R; Peters, A; Heinrich, J; Weinmayr, G; Concin, H; Nagel, G; Ineichen, A; Jacquemin, B; Stempfelet, M; Vilier, A; Ricceri, F; Sacerdote, C; Pedeli, X; Katsoulis, M; Trichopoulou, A; Brunekreef, B; Katsouyanni, K. (2014). Air pollution and nonmalignant respiratory mortality in 16 cohorts within the ESCAPE project. Am J Respir Crit Care Med 189: 684-696. http://dx.doi.org/10.1164/rccm.201310-1777OC

Dominici, F; McDermott, A; Daniels, M; Zeger, SL; Samet, JM. (2005). Revised analyses of the national morbidity, mortality, and air pollution study: Mortality among residents of 90 cities. J Toxicol Environ Health A 68: 1071-1092. http://dx.doi.org/10.1080/15287390590935932

Dominici, F; Peng, RD; Zeger, SL; White, RH; Samet, JM. (2007). Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? Am J Epidemiol 166: 880-888. http://dx.doi.org/10.1093/aje/kwm222

Enstrom, JE. (2017). Fine particulate matter and total mortality in Cancer Prevention Study Cohort reanalysis. Dose-Response 15: 1559325817693345. http://dx.doi.org/10.1177/1559325817693345

Franklin, M; Koutrakis, P; J, S. (2008). The role of particle composition on the association between PM2.5 and mortality. Epidemiology 19: 680-689. http://dx.doi.org/10.1097/EDE.0b013e3181812bb7

Franklin, M; Zeka, A; Schwartz, J. (2007). Association between PM2.5 and all-cause and specific-cause mortality in 27 US communities. J Expo Sci Environ Epidemiol 17: 279-287. http://dx.doi.org/10.1038/sj.jes.7500530

Gan, W; Koehoorn, M; Davies, H; Demers, P; Tamburic, L; Brauer, M. (2011). Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. Environ Health Perspect 119: 501-507. http://dx.doi.org/10.1289/ehp.1002511

Garcia, CA; Yap, PS; Park, HY; Weller, BL. (2015). Association of long-term PM2.5 exposure with mortality using different air pollution exposure models: impacts in rural and urban California. Int J Environ Health Res 26: 1-13. http://dx.doi.org/10.1080/09603123.2015.1061113

Hart, JE; Garshick, E; Dockery, DW; Smith, TJ; Ryan, L; Laden, F. (2011). Long-term ambient multi-pollutant exposures and mortality. Am J Respir Crit Care Med 183: 73-78. http://dx.doi.org/10.1164/rccm.200912-1903OC

Hart, JE; Liao, X; Hong, B; Puett, RC; Yanosky, JD; Suh, H; Kioumourtzoglou, MA; Spiegelman, D; Laden, F. (2015). The association of long-term exposure to PM2.5 on all-cause mortality in the Nurses' Health Study and the impact of measurement-error correction. Environ Health 14: 38. http://dx.doi.org/10.1186/s12940-015-0027-6

Hoek, G; Boogaard, H; Knol, A; de Hartog, J; Slottje, P; Ayres, JG; Borm, P; Brunekreef, B; Donaldson, K; Forastiere, F; Holgate, S; Kreyling, WG; Nemery, B; Pekkanen, J; Stone, V; Wichmann, HE; van der Sluijs, J. (2009). Concentration response functions for ultrafine particles and all-cause mortality and hospital admissions: results of a European Expert Panel elicitation. Environ Sci Technol 44: 476-482. http://dx.doi.org/10.1021/es9021393

Hu, J; Zhang, H; Chen, S; Ying, Q; Wiedinmyer, C; Vandenberghe, F; Kleeman, MJ. (2014a). Identifying PM2.5 and PM0.1 sources for epidemiological studies in California. Environ Sci Technol 48: 4980-4990. http://dx.doi.org/10.1021/es404810z

Hu, J; Zhang, H; Chen, SH; Wiedinmyer, C; Vandenberghe, F; Ying, Q; Kleeman, MJ. (2014b). Predicting primary PM2.5 and PM0.1 trace composition for epidemiological studies in California. Environ Sci Technol 48: 4971-4979. http://dx.doi.org/10.1021/es404809j

Ito, K; Mathes, R; Ross, Z; Nádas, A; Thurston, G; Matte, T. (2011). Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. Environ Health Perspect 119: 467-473. http://dx.doi.org/10.1289/ehp.1002667

Janssen, NAH; Fischer, P; Marra, M; Ameling, C; Cassee, FR. (2013). Short-term effects of PM2.5, PM10 and PM2.5-10 on daily mortality in the Netherlands. Sci Total Environ 463: 20-26. http://dx.doi.org/10.1016/j.scitotenv.2013.05.062

Jerrett, M; Burnett, RT; Beckerman, BS; Turner, MC; Krewski, D; Thurston, G; Martin, RV; van Donkelaar, A; Hughes, E; Shi, Y; Gapstur, SM; Thun, MJ; Pope, CA, III. (2013). Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med 188: 593-599. http://dx.doi.org/10.1164/rccm.201303-0609OC

Jerrett, M; Burnett, RT; Pope, CA, III; Ito, K; Thurston, G; Krewski, D; Shi, Y; Calle, E; Thun, M. (2009). Long-term ozone exposure and mortality. N Engl J Med 360: 1085-1095. http://dx.doi.org/10.1056/NEJMoa0803894

Jerrett, M; Turner, MC; Beckerman, BS; Pope, CA; van Donkelaar, A; Martin, RV; Serre, M; Crouse, D; Gapstur, SM; Krewski, D; Diver, WR; Coogan, PF; Thurston, GD; Burnett, RT. (2016). Comparing the health effects of ambient particulate matter estimated using ground-based versus remote sensing exposure estimates. Environ Health Perspect 125: 552-559. http://dx.doi.org/10.1289/EHP575

Kettunen, J; Lanki, T; Tiittanen, P; Aalto, PP; Koskentalo, T; Kulmala, M; Salomaa, V; Pekkanen, J. (2007). Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. Stroke 38: 918-922. http://dx.doi.org/10.1161/01.STR.0000257999.49706.3b

Kim, SY; Dutton, SJ; Sheppard, L; Hannigan, MP; Miller, SL; Milford, JB; Peel, JL; Vedal, S. (2015). The short-term association of selected components of fine particulate matter and mortality in the Denver Aerosol Sources and Health (DASH) study. Environ Health 14: 49. http://dx.doi.org/10.1186/s12940-015-0037-4

Kioumourtzoglou, MA; Schwartz, J; James, P; Dominici, F; Zanobetti, A. (2016). PM2.5 and mortality in 207 us cities: Modification by temperature and city characteristics. Epidemiology 27: 221-227. http://dx.doi.org/10.1097/EDE.0000000000000422

Klemm, RJ; Mason, R. (2003). Replication of reanalysis of Harvard Six-City mortality study. In HEI Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, Part II. Boston, MA: Health Effects Institute.

Klemm, RJ; Mason, RM, Jr; Heilig, CM; Neas, LM; Dockery, DW. (2000). Is daily mortality associated specifically with fine particles? Data reconstruction and replication of analyses. J Air Waste Manag Assoc 50: 1215-1222.

Kloog, I; Chudnovsky, AA; Just, AC; Nordio, F; Koutrakis, P; Coull, BA; Lyapustin, A; Wang, Y; Schwartz, J. (2014). A new hybrid spatio-temporal model for estimating daily multi-year PM2.5 concentrations across northeastern USA using high resolution aerosol optical depth data. Atmos Environ 95: 581-590. http://dx.doi.org/10.1016/j.atmosenv.2014.07.014

Kloog, I; Koutrakis, P; Coull, BA; Lee, HJ; Schwartz, J. (2011). Assessing temporally and spatially resolved PM2.5 exposures for epidemiological studies using satellite aerosol optical depth measurements. Atmos Environ 45: 6267-6275. http://dx.doi.org/10.1016/j.atmosenv.2011.08.066

Kloog, I; Ridgway, B; Koutrakis, P; Coull, BA; Schwartz, JD. (2013). Long- and short-term exposure to PM2.5 and mortality: Using novel exposure models. Epidemiology 24: 555-561. http://dx.doi.org/10.1097/EDE.0b013e318294beaa

Kollanus, V; Tiittanen, P; Niemi, JV; Lanki, T. (2016). Effects of long-range transported air pollution from vegetation fires on daily mortality and hospital admissions in the Helsinki metropolitan area, Finland. Environ Res 151: 351-358. http://dx.doi.org/10.1016/j.envres.2016.08.003

Koutrakis, P; Suh, HH; Sarnat, JA; Brown, KW; Coull, BA; Schwartz, J. (2005). Characterization of particulate and gas exposures of sensitive subpopulations living in Baltimore and Boston (pp. 1-65; discussion 67-75). Boston, MA: Health Effects Institute.

Krall, JR; Anderson, GB; Dominici, F; Bell, ML; Peng, RD. (2013). Short-term exposure to particulate matter constituents and mortality in a national study of U.S. urban communities. Environ Health Perspect 121: 1148-1153. http://dx.doi.org/10.1289/ehp.1206185

Laden, F; Schwartz, J; Speizer, FE; Dockery, DW. (2006). Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 173: 667-672. http://dx.doi.org/10.1164/rccm.200503-443OC

Lanzinger, S; Schneider, A; Breitner, S; Stafoggia, M; Erzen, I; Dostal, M; Pastorkova, A; Bastian, S; Cyrys, J; Zscheppang, A; Kolodnitska, T; Peters, A. (2016). Associations between ultrafine and fine particles and mortality in five central European cities - Results from the UFIREG study. Environ Int 88: 44-52. http://dx.doi.org/10.1016/j.envint.2015.12.006

Lee, H; Honda, Y; Hashizume, M; Guo, YL; Wu, CF; Kan, H; Jung, K; Lim, YH; Yi, S; Kim, H. (2015a). Short-term exposure to fine and coarse particles and mortality: Amulticity time-series study in East Asia. Environ Pollut 207: 43-51. http://dx.doi.org/10.1016/j.envpol.2015.08.036

Lee, HJ; Liu, Y; Coull, BA; Schwartz, J; Koutrakis, P. (2011). A novel calibration approach of MODIS AOD data to predict PM2.5 concentrations. Atmos Chem Phys 11: 7991-8002. http://dx.doi.org/10.5194/acp-11-7991-2011

Lee, M; Kloog, I; Chudnovsky, A; Lyapustin, A; Wang, Y; Melly, S; Coull, B; Koutrakis, P; Schwartz, J. (2015b). Spatiotemporal prediction of fine particulate matter using high-resolution satellite images in the Southeastern US 2003-2011. J Expo Sci Environ Epidemiol 26: 377-384. http://dx.doi.org/10.1038/jes.2015.41

Lee, M; Koutrakis, P; Coull, B; Kloog, I; Schwartz, J. (2015c). Acute effect of fine particulate matter on mortality in three Southeastern states from 2007-2011. J Expo Sci Environ Epidemiol 26: 173-179. http://dx.doi.org/10.1038/jes.2015.47

Leitte, AM; Schlink, U; Herbarth, O; Wiedensohler, A; Pan, XC; Hu, M; Wehner, B; Breitner, S; Peters, A; Wichmann, HE; Franck, U. (2012). Associations between size-segregated particle number concentrations and respiratory mortality in Beijing, China. Int J Environ Health Res 22: 119-133. http://dx.doi.org/10.1080/09603123.2011.605878

Lepeule, J; Laden, F; Dockery, D; Schwartz, J. (2012). Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. Environ Health Perspect 120: 965-970. http://dx.doi.org/10.1289/ehp.1104660

Li, Y; Ma, Z; Zheng, C; Shang, Y. (2015). Ambient temperature enhanced acute cardiovascular-respiratory mortality effects of PM2.5 in Beijing, China. Int J Biometeorol 59: 1761-1770. http://dx.doi.org/10.1007/s00484-015-0984-z

Lin, H; Liu, T; Xiao, J; Zeng, W; Guo, L; Li, X; Xu, Y; Zhang, Y; Chang, JJ; Vaughn, MG; Qian, ZM; Ma, W. (2016). Hourly peak PM2.5 concentration associated with increased cardiovascular mortality in Guangzhou, China. J Expo Sci Environ Epidemiol 27: 333-338. http://dx.doi.org/10.1038/jes.2016.63

Lipfert, FW; Wyzga, RE; Baty, JD; Miller, JP. (2006). Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: Long-term mortality in a cohort of US veterans. Atmos Environ 40: 154-169. http://dx.doi.org/10.1016/j.atmosenv.2005.09.027

Lippmann, M; Chen, LC; Gordon, T; Ito, K; Thurston, GD. (2013a). National Particle Component Toxicity (NPACT) Initiative: Integrated epidemiologic and toxicologic studies of the health effects of particulate matter components: Investigators' Report [HEI] (pp. 5-13). (177). Boston, MA: Health Effects Institute.

Lippmann, M; Chen, LC; Gordon, T; Ito, K; Thurston, GD. (2013b). National Particle Component Toxicity (NPACT) initiative: Study 3. Time-series analysis of mortality, hospitalizations, and ambient PM2.5 and its components. Appendix G. Supplemental information [HEI]. (177). Boston, MA: Health Effects Institute. https://www.healtheffects.org/system/files/RR177-Lippmann-Study3-AppendixG_0.pdf

Lipsett, MJ; Ostro, BD; Reynolds, P; Goldberg, D; Hertz, A; Jerrett, M; Smith, DF; Garcia, C; Chang, ET; Bernstein, L. (2011). Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. Am J Respir Crit Care Med 184: 828-835. http://dx.doi.org/10.1164/rccm.201012-2082OC

Liu, S; Zhang, K. (2015). Fine particulate matter components and mortality in Greater Houston: Did the risk reduce from 2000 to 2011? Sci Total Environ 538: 162-168. http://dx.doi.org/10.1016/j.scitotenv.2015.08.037

Madsen, C; Rosland, P; Hoff, DA; Nystad, W; Nafstad, P; Naess, OE. (2012). The short-term effect of 24-h average and peak air pollution on mortality in Oslo, Norway. Eur J Epidemiol 27: 717-727. http://dx.doi.org/10.1007/s10654-012-9719-1

Malig, BJ; BD, O. (2009). Coarse particles and mortality: evidence from a multi-city study in California. Occup Environ Med 66: 832-839. http://dx.doi.org/10.1136/oem.2008.045393

McDonnell, WF; Nishino-Ishikawa, N; Petersen, FF; Chen, LH; Abbey, DE. (2000). Relationships of mortality with the fine and coarse fractions of long-term ambient PM10 concentrations in nonsmokers. J Expo Anal Environ Epidemiol 10: 427-436. http://dx.doi.org/10.1038/sj.jea.7500095

Meng, X, ia; Ma, Y; Chen, R; Zhou, Z; Chen, B; Kan, H. (2013). Size-Fractionated Particle Number Concentrations and Daily Mortality in a Chinese City. Environ Health Perspect 121: 1174-1178. http://dx.doi.org/10.1289/ehp.1206398

Miller, KA; Siscovick, DS; Sheppard, L; Shepherd, K; Sullivan, JH; Anderson, GL; Kaufman, JD. (2007). Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356: 447-458. http://dx.doi.org/10.1056/NEJMoa054409

Mostofsky, E; Schwartz, J; Coull, BA; Koutrakis, P; Wellenius, GA; Suh, HH; Gold, DR; Mittleman, MA. (2012). Modeling the association between particle constituents of air pollution and health outcomes. Am J Epidemiol 176: 317-326. http://dx.doi.org/10.1093/aje/kws018

Naess, O; Nafstad, P; Aamodt, G; Claussen, B; Rosland, P. (2007). Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. Am J Epidemiol 165: 435-443. http://dx.doi.org/10.1093/aje/kwk016

NHLBI (National Institutes of Health, National Heart Lung and Blood Institute). (2017). NHLBI fact book, fiscal year 2012: Disease statistics. Available online at https://www.nhlbi.nih.gov/about/documents/factbook/2012/chapter4 (accessed August 23, 2017).

Oftedal, B; Walker, S; Gram, F; McInnes, H; Nafstad, P. (2009). Modelling long-term averages of local ambient air pollution in Oslo, Norway: evaluation of nitrogen dioxide, PM10 and PM2.5. Int J Environ Pollut 36: 110-126. http://dx.doi.org/10.1504/IJEP.2009.021820

Ostro, B; Broadwin, R; Green, S; Feng, WY; Lipsett, M. (2006). Fine particulate air pollution and mortality in nine California counties: Results from CALFINE. Environ Health Perspect 114: 29-33. http://dx.doi.org/10.1289/ehp.8335

Ostro, B; Feng, WY; Broadwin, R; Green, S; Lipsett, M. (2007). The effects of components of fine particulate air pollution on mortality in California: Results from CALFINE. Environ Health Perspect 115: 13-19. http://dx.doi.org/10.1289/ehp.9281

Ostro, B; Hu, J; Goldberg, D; Reynolds, P; Hertz, A; Bernstein, L; Kleeman, MJ. (2015). Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California teachers study cohort. Environ Health Perspect 123: 549-556. http://dx.doi.org/10.1289/ehp.1408565

Ostro, B; Lipsett, M; Reynolds, P; Goldberg, D; Hertz, A; Garcia, C; Henderson, KD; Bernstein, L. (2010). Long-term exposure to constituents of fine particulate air pollution and mortality: Results from the California teachers study. Environ Health Perspect 118: 363-369. http://dx.doi.org/10.1289/ehp.0901181

Ostro, BD; Feng, WY; Broadwin, R; Malig, BJ; Green, RS; Lipsett, MJ. (2008). The impact of components of fine particulate matter on cardiovascular mortality in susceptible subpopulations. Occup Environ Med 65: 750-756. http://dx.doi.org/10:1136/oem.200T036673

Paciorek, CJ; Yanosky, JD; Puett, RC; Laden, F; Suh, HH. (2009). Practical large-scale spatio-temporal modeling of particulate matter concentrations. Ann Appl Stat 3: 370-397. http://dx.doi.org/10.1214/08-AOAS204

Pascal, M; Falq, G; Wagner, V; Chatignoux, E; Corso, M; Blanchard, M; Host, S; Pascal, L; Larrieu, S. (2014). Short-term impacts of particulate matter (PM10, PM10-2.5, PM2.5) on mortality in nine French cities. Atmos Environ 95: 175-184. http://dx.doi.org/10.1016/j.atmosenv.2014.06.030

Pererz, L; Medina-Ramon, M; Kunzli, N; Alastuey, A; Pey, J; Perez, N; Garcia, R; Tobias, A; Querol, X; Sunyer, J. (2009). Size fractionate particulate matter, vehicle traffic, and case-specific daily mortality in Barcelona, Spain. Environ Sci Technol 43: 4707-4714. http://dx.doi.org/10.1021/es8031488

Pinault, L; Tjepkema, M; Crouse, DL; Weichenthal, S; van Donkelaar, A; Martin, RV; Brauer, M; Chen, H; Burnett, RT. (2016). Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. Environ Health 15: Article #18. http://dx.doi.org/10.1186/s12940-016-0111-6

Pope, CA, III; Ezzati, M; Dockery, DW. (2009). Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 360: 376-386. http://dx.doi.org/10.1056/NEJMsa0805646

Pope, CA, III; Thun, MJ; Namboodiri, MM; Dockery, DW; Evans, JS; Speizer, FE; Heath, CW, Jr. (1995). Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151: 669-674. http://dx.doi.org/10.1164/ajrccm/151.3_Pt_1.669

Pope, CA; Turner, MC; Burnett, R; Jerrett, M; Gapstur, SM; Diver, WR; Krewski, D; Brook, RD. (2014). Relationships between fine particulate air pollution, cardiometabolic disorders and cardiovascular mortality. Circ Res 116: 108-U258. http://dx.doi.org/10.1161/CIRCRESAHA.116.305060

Puett, RC; Hart, JE; Suh, H; Mittleman, M; Laden, F. (2011). Particulate matter exposures, mortality and cardiovascular disease in the health professionals follow-up study. Environ Health Perspect 119: 1130-1135. http://dx.doi.org/10.1289/ehp.1002921

Puett, RC; Hart, JE; Yanosky, JD; Paciorek, C; Schwartz, J; Suh, H; Speizer, FE; Laden, F. (2009). Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. Environ Health Perspect 117: 1697-1701. http://dx.doi.org/10.1289/ehp.0900572

Sacks, JD; Ito, K; Wilson, WE; Neas, LM. (2012). Impact of covariate models on the assessment of the air pollution-mortality association in a single- and multipollutant context. Am J Epidemiol 176: 622-634. http://dx.doi.org/10.1093/aje/kws135

Samoli, E; Analitis, A; Touloumi, G; Schwartz, J; Anderson, HR; Sunyer, J; Bisanti, L; Zmirou, D; Vonk, JM; Pekkanen, J; Goodman, P; Paldy, A; Schindler, C; Katsouyanni, K. (2005). Estimating the exposure-response relationships between particulate matter and mortality within the APHEA multicity project. Environ Health Perspect 113: 88-95.

Samoli, E; Atkinson, RW; Analitis, A; Fuller, GW; Beddows, D; Green, DC; Mudway, IS; Harrison, RM; Anderson, HR; Kelly, FJ. (2016). Differential health effects of short-term exposure to source-specific particles in London, U.K. Environ Int 97: 246-253. http://dx.doi.org/10.1016/j.envint.2016.09.017

Samoli, E; Stafoggia, M; Rodopoulou, S; Ostro, B; Declercq, C; Alessandrini, E; Díaz, J; Karanasiou, A; Kelessis, AG; Le Tertre, A; Pandolfi, P; Randi, G; Scarinzi, C; Zauli-Sajani, S; Katsouyanni, K; Forastiere, F; group, tMS. (2013). Associations between Fine and Coarse Particles and Mortality in Mediterranean Cities: Results from the MED-PARTICLES Project. Environ Health Perspect 121: 932-938. http://dx.doi.org/10.1289/ehp.1206124

Schwartz, J. (2000). Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. Environ Health Perspect 108: 563-568.

Schwartz, J; Austin, E; Bind, MA; Zanobetti, A; Koutrakis, P. (2015). Estimating causal associations of fine particles with daily deaths in Boston. Am J Epidemiol 182: 644-650. http://dx.doi.org/10.1093/aje/kwv101

Schwartz, J; Bind, MA; Koutrakis, P. (2017). Estimating causal effects of local air pollution on daily deaths: Effect of low levels. Environ Health Perspect 125: 23-29. http://dx.doi.org/10.1289/EHP232

Schwartz, J; Coull, B; Laden, F; Ryan, L. (2008). The effect of dose and timing of dose on the association between airborne particles and survival. Environ Health Perspect 116: 64-69. http://dx.doi.org/10.1289/ehp.9955

Schwartz, J; Zanobetti, A; Bateson, T. (2003). Morbidity and mortality among elderly residents of cities with daily PM measurements. Boston: Health Effects Institute. http://www.healtheffects.org/Pubs/TimeSeries.pdf

Shi, L; Zanobetti, A; Kloog, I; Coull, BA; Koutrakis, P; Melly, SJ; Schwartz, JD. (2015). Low-concentration PM2.5 and mortality: estimating acute and chronic effects in a population-based study. Environ Health Perspect 124: 46-52. http://dx.doi.org/10.1289/ehp.1409111

Stafoggia, M; Schneider, A; Cyrys, J; Samoli, E; Andersen, ZJ; Bedada, GB; Bellander, T; Cattani, G; Eleftheriadis, K; Faustini, A; Hoffmann, B; Jacquemin, B; Katsouyanni, K; Massling, A; Pekkanen, J; Perez, N; Peters, A; Quass, U; Yli-Tuomi, T; Forastiere, F. (2017). Association between short-term exposure to ultrafine particles and mortality in eight European urban areas. Epidemiology 28: 172-180. http://dx.doi.org/10.1097/EDE.0000000000000599

Stölzel, M; Breitner, S; Cyrys, J; Pitz, M; Wolke, G; Kreyling, W; Heinrich, J; Wichmann, HE; Peters, A. (2007). Daily mortality and particulate matter in different size classes in Erfurt, Germany. J Expo Sci Environ Epidemiol 17: 458-467. http://dx.doi.org/10.1038/sj.jes.7500538

Sun, S; Cao, P; Chan, KP; Tsang, H; Wong, CM; Thach, TQ. (2015). Temperature as a modifier of the effects of fine particulate matter on acute mortality in Hong Kong. Environ Pollut 205: 357-364. http://dx.doi.org/10.1016/j.envpol.2015.06.007

Thurston, GD; Ahn, J; Cromar, KR; Shao, Y; Reynolds, HR; Jerrett, M; Lim, CC; Shanley, R; Park, Y; Hayes, RB. (2015). Ambient particulate matter air pollution exposure and mortality in the NIH-AARP Diet and Health Cohort. Environ Health Perspect 124: 484-490. http://dx.doi.org/10.1289/ehp.1509676

Thurston, GD; Burnett, RT; Turner, MC; Shi, Y; Krewski, D; Lall, R; Ito, K; Jerrett, M; Gapstur, SM; Diver, WR; Pope, CA, III. (2016). Ischemic heart disease mortality and long-term exposure to source-related components of U.S. fine particle air pollution. Environ Health Perspect 124: 785-794. http://dx.doi.org/10.1289/ehp.1509777

Tonne, C; Halonen, JI; Beevers, SD; Dajnak, D; Gulliver, J; Kelly, FJ; Wilkinson, P; Anderson, HR. (2015). Long-term traffic air and noise pollution in relation to mortality and hospital readmission among myocardial infarction survivors. Int J Hyg Environ Health 219: 72-78. http://dx.doi.org/10.1016/j.ijheh.2015.09.003

Turner, MC; Cohen, A; Burnett, RT; Jerrett, M; Diver, WR; Gapstur, SM; Krewski, D; Samet, JM; Pope, CA. (2017). Interactions between cigarette smoking and ambient PM2.5 for cardiovascular mortality. Environ Res 154: 304-310. http://dx.doi.org/10.1016/j.envres.2017.01.024

Turner, MC; Jerrett, M; Pope, A, III; Krewski, D; Gapstur, SM; Diver, WR; Beckerman, BS; Marshall, JD; Su, J; Crouse, DL; Burnett, RT. (2016). Long-term ozone exposure and mortality in a large prospective study. Am J Respir Crit Care Med 193: 1134-1142. http://dx.doi.org/10.1164/rccm.201508-1633OC

U.S. EPA (U.S. Environmental Protection Agency). (1996). Air quality criteria for particulate matter, volume 1 of 3 [EPA Report]. (EPA/600/P-95/001aF). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (2004). Air quality criteria for particulate matter [EPA Report]. (EPA/600/P-99/002aF-bF). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environemntal Assessment- RTP Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=87903

U.S. EPA (U.S. Environmental Protection Agency). (2008). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843

U.S. EPA (U.S. Environmental Protection Agency). (2009). Integrated science assessment for particulate matter [EPA Report]. (EPA/600/R-08/139F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546

U.S. EPA (U.S. Environmental Protection Agency). (2015a). Integrated science assessment for sulfur oxides - Health criteria (external review draft) [EPA Report]. (EPA/600/R-15/066). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Asseessment. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310044

U.S. EPA (U.S. Environmental Protection Agency). (2015b). Preamble to the integrated science assessments [EPA Report]. (EPA/600/R-15/067). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, RTP Division. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244

U.S. EPA (U.S. Environmental Protection Agency). (2016). Integrated science assessment for oxides of nitrogen-Health Criteria (final report) [EPA Report]. (EPA/600/R-15/068). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=526855

U.S. EPA (U.S. Environmental Protection Agency). (2018a). Supplementary material for chapter 11 (mortality) of the integrated science assessment for particulate matter.

U.S. EPA (U.S. Environmental Protection Agency). (2018b). Supplementary material: Chapter 11 (mortality) of the integrated science assessment for particulate matter.

Ueda, K; Nitta, H; Ono, M; Takeuchi, A. (2009). Estimating mortality effects of fine particulate matter in Japan: A comparison of time-series and case-crossover analyses. J Air Waste Manag Assoc 59: 1212-1218. http://dx.doi.org/10.3155/1047-3289.59.10.1212

van Donkelaar, A; Martin, RV; Brauer, M; Kahn, R; Levy, R; Verduzco, C; Villeneuve, PJ. (2010). Global estimates of ambient fine particulate matter concentrations from satellite-based aerosol optical depth: development and application. Environ Health Perspect 118: 847-855. http://dx.doi.org/10.1289/ehp.0901623

van Donkelaar, A; Martin, RV; Spurr, RJ; Burnett, RT. (2015). High-resolution satellite-derived PM2.5 from optimal estimation and geographically weighted regression over North America. Environ Sci Technol 49: 10482-10491. http://dx.doi.org/10.1021/acs.est.5b02076

Villeneuve, PJ; Weichenthal, SA; Crouse, D; Miller, AB; To, T; Martin, RV; van Donkelaar, A; Wall, C; Burnett, RT. (2015). Long-term exposure to fine particulate matter air pollution and mortality among Canadian women. Epidemiology 26: 536-545. http://dx.doi.org/10.1097/EDE.0000000000000294

Wang, Y; Kloog, I; Coull, BA; Kosheleva, A; Zanobetti, A; Schwartz, JD. (2016). Estimating causal effects of long-term PM2.5 exposure on mortality in New Jersey. Environ Health Perspect 124: 1182-1188. http://dx.doi.org/10.1289/ehp.1409671

Wang, Y; Lee, M; Liu, P; Shi, L; Yu, Z; Abu Awad, Y; Zanobetti, A; Schwartz, JD. (2017a). Doubly robust additive hazards models to estimate effects of a continuous exposure on survival. Epidemiology 28: 771-779. http://dx.doi.org/10.1097/EDE.0000000000000742

Wang, Y; Shi, L; Lee, M; Liu, P; Di, Q; Zanobetti, A; Schwartz, JD. (2017b). Long-term exposure to PM2.5 and mortality among older adults in the Southeastern US. Epidemiology 28: 207-214. http://dx.doi.org/10.1097/EDE.0000000000000614

Weichenthal, S; Crouse, DL; Pinault, L; Godri-Pollitt, K; Lavigne, E; Evans, G; van Donkelaar, A; Martin, RV; Burnett, RT. (2016). Oxidative burden of fine particulate air pollution and risk of cause-specific mortality in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Res 146: 92-99. http://dx.doi.org/10.1016/j.envres.2015.12.013

Weichenthal, S; Villeneuve, PJ; Burnett, RT; van Donkelaar, A; Martin, RV; Jones, RR; Dellavalle, CT; Sandler, DP; Ward, MH; Hoppin, JA. (2014). Long-term exposure to fine particulate matter: association with nonaccidental and cardiovascular mortality in the agricultural health study cohort. Environ Health Perspect 122: 609-615. http://dx.doi.org/10.1289/ehp.1307277

Welty, LJ; Zeger, SL. (2005). Are the acute effects of particulate matter on mortality in the National Morbidity, Mortality, and Air Pollution study the result of inadequate control for weather and season? A sensitivity analysis using flexible distributed lag models. Am J Epidemiol 162: 80-88. http://dx.doi.org/10.1093/aje/kwi157

Wolf, K; Stafoggia, M; Cesaroni, G; Andersen, ZJ; Beelen, R; Galassi, C; Hennig, F; Migliore, E; Penell, J; Ricceri, F; Sørensen, M; Turunen, AW; Hampel, R; Hoffmann, B; Kälsch, H; Laatikainen, T; Pershagen, G; Raaschou-Nielsen, O; Sacerdote, C; Vineis, P; Badaloni, C; Cyrys, J; de Hoogh, K; Eriksen, KT; Jedynska, A; Keuken, M; Kooter, I; Lanki, T; Ranzi, A; Sugiri, D; Tsai, MY; Wang, M; Hoek, G; Brunekreef, B; Peters, A; Forastiere, F. (2015). Long-term exposure to particulate matter constituents and the incidence of coronary events in 11 European cohorts. Epidemiology 26: 565-574. http://dx.doi.org/10.1097/EDE.0000000000000300

Wong, CM; Lai, HK; Tsang, H; Thach, TQ; Thomas, GN; Lam, KB; Chan, KP; Yang, L; Lau, AK; Ayres, JG; Lee, SY; Chan, WM; Hedley, AJ; Lam, TH. (2015). Satellite-Based Estimates of Long-Term Exposure to Fine Particles and Association with Mortality in Elderly Hong Kong Residents. Environ Health Perspect 123: 1167-1172. http://dx.doi.org/10.1289/ehp.1408264

Yanosky, JD; Paciorek, CJ; Laden, F; Hart, JE; Puett, RC; Liao, D; Suh, HH. (2014). Spatio-temporal modeling of particulate air pollution in the conterminous United States using geographic and meteorological predictors. Environ Health 13: 63. http://dx.doi.org/10.1186/1476-069X-13-63

Yanosky, JD; Paciorek, CJ; Suh, HH. (2009). Predicting chronic fine and coarse particulate exposures using spatiotemporal models for the northeastern and midwestern United States. Environ Health Perspect 117: 522-529. http://dx.doi.org/10.1289/ehp.11692

Yorifuji, T; Kashima, S; Doi, H. (2016). Fine-particulate air pollution from diesel emission control and mortality rates in Tokyo: a quasi-experimental study. Epidemiology 27: 769-778. http://dx.doi.org/10.1097/EDE.0000000000000546

Young, SS; Smith, RL; Lopiano, KK. (2017). Air quality and acute deaths in California, 2000-2012. Regul Toxicol Pharmacol 88: 173-184. http://dx.doi.org/10.1016/j.yrtph.2017.06.003

Zanobetti, A; Austin, E; Coull, BA; Schwartz, J; Koutrakis, P. (2014a). Health effects of multi-pollutant profiles. Environ Int 71: 13-19. http://dx.doi.org/10.1016/j.envint.2014.05.023

Zanobetti, A; Dominici, F; Wang, Y, un; Schwartz, JD. (2014b). A national case-crossover analysis of the short-term effect of PM2.5 on hospitalizations and mortality in subjects with diabetes and neurological disorders. Environ Health 13: 38. http://dx.doi.org/10.1186/1476-069X-13-38

Zanobetti, A; Schwartz, J. (2008). Temperature and mortality in nine us cities. Epidemiology 1: 563-570. http://dx.doi.org/10.1097/EDE.0b013e31816d652d

Zanobetti, A; Schwartz, J. (2009). The effect of fine and coarse particulate air pollution on mortality: A national analysis. Environ Health Perspect 117: 1-40. http://dx.doi.org/10.1289/ehp.0800108

Zhou, J; Ito, K; Lall, R; Lippmann, M; Thurston, G. (2011). Time-series analysis of mortality effects of fine particulate matter components in Detroit and Seattle. Environ Health Perspect 119: 461-466. http://dx.doi.org/10.1289/ehp.1002613

CHAPTER 12 POPULATIONS AND LIFESTAGES POTENTIALLY AT INCREASED RISK OF A PARTICULATE MATTER-RELATED HEALTH EFFECT

Summary of Populations and Lifestages Potentially at Increased Risk of a Particulate Matter-Related Health Effect

- The preceding health effects chapters in this ISA characterized a large body of evidence examining $PM_{2.5}$-related health effects and demonstrate that there is strong evidence for a range of health effects due to short- and long-term $PM_{2.5}$ exposures that are observed in both the general population as well as specific populations (e.g., people with a pre-existing disease) and lifestages (i.e., children and older adults). ***Thus, extensive evidence in the health effects chapters indicates that both the general population as well as specific populations and lifestages are at risk for $PM_{2.5}$-related health effects.***
- More specific consideration is often given to specific lifestages and populations, such as children, those with pre-existing diseases, or certain sociodemographic characteristic (e.g., low socioeconomic status) to determine if these unique populations and lifestages might be at increased risk of an air pollutant-related health effect relative to others in the population that do not have that characteristic.
- While preceding chapters focus on whether there is evidence broadly of $PM_{2.5}$-related health effects, the objective of this chapter is to evaluate the extent to which the evidence indicates that a population or lifestage is at **disproportionately greater risk,** using an established framework to assess the available evidence. ***Thus, this chapter is addressing the specific question: are specific populations or lifestages at increased risk of a $PM_{2.5}$-related health effect compared to a reference population?***
- In addressing this question, the evaluation builds on evidence from the 2009 PM ISA and takes into consideration a broad range of recent evidence from epidemiologic, controlled human exposure, and animal toxicological studies, in addition to information on differential exposure or dosimetry. Conclusions are drawn based on an integrated evaluation of evidence in the context of the framework.

12.1 Introduction

The NAAQS are intended to protect public health with an adequate margin of safety, which includes protection for the population as a whole and for those groups potentially at increased risk for health effects in response to exposure to a criteria air pollutant (e.g., PM) [see Preamble to the ISA (U.S. EPA, 2015b)]. There is interindividual variation in both physiological responses, as well as exposures to ambient air pollution. A variety of terms have been used in the scientific literature to describe risk factors and subsequently populations or lifestages that may be at increased risk of an air pollutant-related health effect, including susceptible, vulnerable, sensitive, at risk, and response-modifying factor (Vinikoor-Imler

et al., 2014) [see Preamble to the ISA (U.S. EPA, 2015b)]. Acknowledging the inconsistency in definitions for these terms across the scientific literature and the lack of a consensus on terminology in the scientific community, "at-risk is the all-encompassing term used within this chapter for groups with specific factors that increase the risk of an air pollutant (e.g., PM)-related health effect in a population", as initially detailed in the 2013 O_3 ISA (U.S. EPA, 2013b). Therefore, while there is strong evidence for health effects to occur in the exposed general population and in some specific populations or lifestages, this chapter focuses on the evaluation and characterization of evidence informing if there are populations or lifestages potentially at increased risk of a PM-related health effect with specific emphasis on studies that compare responses to a reference population, where appropriate [see Preamble to the ISA (U.S. EPA, 2015b)].

As discussed in the Preamble to the ISAs (U.S. EPA, 2015b), the risk of health effects from exposure to an ambient air pollutant, including PM, may be modified as a result of intrinsic (e.g., pre-existing disease, genetic factors) or extrinsic factors (e.g., sociodemographic or behavioral factors), differences in internal dose (e.g., due to variability in ventilation rates or exercise behaviors), or differences in exposure to air pollutant concentrations (e.g., more time spent in areas with higher ambient concentrations). For the purposes of informing decisions on the NAAQS, the focus of this chapter is on identifying those populations or lifestages at increased risk of a PM-related health effect. It is recognized that, in many cases, subsets of the population are at increased risk of a PM-related health effect due to a combination or co-occurrence of factors [e.g., residential location and socioeconomic status (SES)], but evidence on the interaction among factors remains very limited. Thus, the following sections identify, evaluate, and characterize the overall confidence that individual factors potentially result in increased risk for PM-related health effects [see Preamble to the ISAs (U.S. EPA, 2015b)].

The preceding chapters of this ISA focus on assessing whether exposure to PM of various size fractions is causally related to health effects regardless of population or lifestage. It is the collective body of evidence spanning populations and lifestages that ultimately forms the basis of the causality determinations detailed within each of the health chapters. These chapters clearly conclude that there is a large body of evidence that demonstrates health effects with PM, particularly $PM_{2.5}$, across populations with diverse characteristics (e.g., children, older adults, people with a pre-existing cardiovascular disease, etc.). While the health chapters assess the degree to which there is evidence of a causal relationship between PM exposure and health effects, this chapter is focusing solely on the question: ***Are there specific populations and lifestages at increased risk of a PM-related health effect compared to a reference population?***

This analysis is one aspect to be considered in the latter evaluation of the extent to which the NAAQS provide public health protection with an adequate margin of safety.

12.2 Approach to Evaluating and Characterizing the Evidence for Populations or Lifestages Potentially at Increased Risk

The systematic approach used to identify, evaluate, and characterize evidence for factors that may increase the risk of a population or specific lifestage to an air pollutant-related health effect, including PM, is described in more detail in the Preamble (U.S. EPA, 2015b). The evidence evaluated in this chapter includes relevant studies discussed in Chapters 5-11 of this ISA relevant to the evaluation of populations and lifestages potentially at increased risk of a PM-related health effect and builds on the evidence presented in the 2009 PM ISA (U.S. EPA, 2009). The evaluation of the evidence focuses on those health outcomes and size fractions of PM for which a "*causal*" or "*likely to be a causal*" relationship was concluded in Chapters 5-11 of this ISA with additional supporting evidence from studies of health outcomes for which the causality determination is "suggestive" or "inadequate". More specifically, this chapter focuses on the health effects related to $PM_{2.5}$ based on the strength of the evidence as described in the health chapters. In addition, focus is given to the endpoints (e.g., mortality, asthma exacerbation, lung development, etc.) that formed the basis of the conclusions. In addition, it is important to recognize that the 2009 PM ISA (U.S. EPA, 2015b) focused broadly on the extent to which evidence indicated that certain populations or lifestages were "susceptible" to a PM-related health effect, regardless of size fraction. As part of the 2013 O_3 ISA (U.S. EPA, 2013a), a framework was developed to systematically evaluate the collective body of evidence and inform whether a specific population or lifestage is at increased risk for an air pollutant-related health effect compared to a reference population, where applicable[82]. As such, it is important to note that the conclusions detailed within this ISA are more nuanced than the dichotomous conclusions of whether a population or lifestage is susceptible for a PM-related health effect as reflected in the 2009 PM ISA (U.S. EPA, 2009).

As described in the Preamble and the PM IRP and demonstrated in previous ISAs (U.S. EPA, 2017, 2016a, b, 2015a, 2013a, b), evidence is integrated across scientific disciplines (i.e., epidemiology, controlled human exposure, and animal toxicology) and health effects, and when available, with relevant dosimetric information (Chapter 4) as well as exposure differences (Chapter 3) in the evaluation process. Epidemiologic studies that include stratified analyses to compare populations or lifestages exposed to similar $PM_{2.5}$ concentrations within the same study design directly inform the question of disproportionate risk. A more detailed presentation of this evidence is included in a supplement to this chapter (U.S. EPA, 2018). Other epidemiologic studies that do not stratify results but instead examine a specific population or lifestage can provide further evidence of increased risk particularly when a health effect is only relevant for a unique population or lifestage (e.g., lung function development in children). When evaluating results

[82] In some cases, studies do not include a reference population for comparison because there are outcomes that are only relevant to some specific populations and lifestages. For example, lung function development is only examined in studies of children because this outcome cannot be measured in adults as lung development is already complete. Another example is studies of asthma hospitalization or emergency department visits, where studies often examine these events only for the population with asthma because those without asthma would not have an asthma exacerbation.

across epidemiologic studies, similar to the characterization of epidemiologic evidence in Chapters 5-11, statistical significance is not the sole criterion by which effect modification and evidence of increased risk is determined; emphasis is placed on patterns or trends in results across these epidemiologic studies.[83] Experimental studies in human subjects or animal models that focus on factors, such as genetic background or health status (e.g., pre-existing asthma), are also important lines of evidence to evaluate to establish coherence of effects across disciplines. These studies can also inform the independent effects of PM as well as biological plausibility of effects observed in epidemiologic studies. Additionally, dosimetry studies can further inform biological plausibility by demonstrating whether the deposition of PM within the body might vary in a particular population or lifestage. Differential exposure to PM in populations and lifestages is also considered when available, though these types of evidence tend to be sparser.

As stated, the objective of this chapter is to identify, evaluate, and characterize the extent to which various factors may increase the risk of a PM-related health effect in a population or lifestage compared to a reference population, where applicable, building on the conclusions drawn in previous chapters in the ISA. More specifically, Table 12-1 presents the framework applied to the available evidence in drawing conclusions on increased risk. The broad categories of factors evaluated include pre-existing disease (Section 12.3), genetic background (Section 12.4), sociodemographic factors (Section 12.5), and behavioral and other factors (see Section 12.6). Furthermore, factors that are considered in this chapter are not predetermined, but are included based on the availability of evidence in the scientific literature. The classifications of evidence are characterized in Table 12-1. A summary of the characterization of the evidence for each factor considered within this chapter is presented in Section 12.7.

It is important to note that while a broad range of evidence is evaluated, there are uncertainties and limitations inherent in the approach used within this chapter to identify populations or lifestages potentially at disproportionately increased risk of a PM-related health effect. First, publication bias, or the tendency not to report quantitatively null results in epidemiologic studies is more frequent in stratified results than main effects, and this can introduce uncertainty when evaluating increased risk or risk modification in general. However, in the evaluation and characterization of the evidence within this chapter, where the evidence is considered "adequate" to classify a group as being at increased risk (Table 12-1) even when considering the strengths and limitations, the collective body of evidence is strong enough to outweigh this uncertainty. In addition, there is variability in the indicators or metrics used to define the populations and/or lifestages that are examined, which can be an important limitation (e.g., well-controlled vs. uncontrolled pre-existing disease, body mass index, indicators of socioeconomic status, various age ranges). Another aspect to consider is variability within the populations or lifestages, such as behavioral differences, biological differences (e.g. obese vs. non-obese), and adherence to treatment for pre-existing disease). These limitations and uncertainties can impact the extent to which the

[83] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations or a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations, unless otherwise noted.

evidence can reliably indicate whether there is disproportionate risk in a population or lifestage compared to a reference population and is considered where relevant.

Table 12-1 Characterization of evidence for factors potentially increasing the risk for particulate matter-related health effects.

Classification	Health Effects
Adequate evidence	There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, this evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.
Suggestive evidence	The collective evidence suggests that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
Inadequate evidence	The collective evidence is inadequate to determine whether a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion to be drawn.
Evidence of no effect	There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, the evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.

12.3 Pre-Existing Diseases/Conditions

Individuals with pre-existing disease may be considered at greater risk of an air pollution-related health effect than those without disease because they are likely in a compromised biological state that can vary depending on the disease and severity. The 2009 PM ISA (U.S. EPA, 2009) concluded that those with pre-existing cardiovascular (CV) and respiratory diseases are generally more susceptible to the health effects associated with exposure to PM, but that evidence for diabetes and obesity was limited. Of the recent epidemiologic studies evaluating effect measure modification by pre-existing disease or condition, most focused on pre-existing CV disease (Section 12.3.1), pre-existing diabetes and metabolic syndrome (Section 12.3.2), obesity (Section 12.3.3), elevated cholesterol (Section 12.3.4), and pre-existing respiratory disease (Section 12.3.5). Table 12-2 presents the prevalence of these diseases from the National Health Interview Survey conducted by the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics (Blackwell and Villarroel, 2018), including the proportion of adults with a current diagnosis categorized by age and geographic region. The large proportions of the U.S. population affected by many chronic diseases, including various cardiovascular diseases, indicates

the potential public health impact, and thus, the importance of characterizing if certain subpopulations may be at increased risk for $PM_{2.5}$-related health effects.

Table 12-2 Prevalence of cardiovascular diseases, diabetes, obesity, and respiratory diseases among adults by age and region in the U.S. in 2016.

	Adults (18+)	Age (%)[a]				Region (%)[b]			
Chronic Disease/Condition	N (in thousands)	18–44	45–64	65–74	75+	North east	Midwest	South	West
All (N, in thousands)	245,142	113,401	83,703	28, 532	19,507	44,851	54,359	87,402	58,531
Selected cardiovascular diseases/conditions									
All heart disease	28,064	3.8	12.2	22.6	36.5	10.2	11.8	11.0	9.4
Coronary heart disease	15,230	1.2	6.0	13.9	25.1	5.4	6.4	6.3	4.5
Hypertension	66,443	9.2	34.4	55.7	59.1	23.5	26.0	27.0	21.9
Stroke	7,449	0.6	3.2	6.6	11.1	2.4	2.5	3.2	2.8
Metabolic disorders/conditions									
Diabetes	23,104	2.8	12.5	23.0	19.4	8.5	9.3	9.3	7.9
Obesity (BMI ≥30 kg/m^2)	70,723	27.5	34.7	31.5	21.2	25.9	33.4	32.1	24.6
Overweight (BMI 25–30 kg/m^2)	82,870	31.8	36.9	40.5	38.3	35.8	33.1	34.2	35.8
Selected respiratory diseases									
Asthmatic	20,383	8.1	9.2	8.3	6.0	9.4	9.0	7.3	8.3
COPD—chronic bronchitis	8,940	2.0	5.0	5.3	4.9	3.1	3.7	4.0	2.6
COPD—emphysema	3,524	0.2	1.8	3.6	4.0	1.2	1.5	1.4	0.9

BMI = body mass index; COPD = chronic obstructive pulmonary disease.

[a]Percentage of individual adults within each age group with disease, based on N (at the top of each age column).

[b]Percentage of individual adults (18+) within each geographic region with disease, based on N (at the top of each region column).

[c]Asthma prevalence is reported for "still has asthma."

Source: Blackwell and Villarroel (2018); National Center for Health Statistics, Summary Health Statistics: National Health Interview Survey, 2016.

12.3.1 Cardiovascular Disease

Overview

- Approximately 12% of adults in the U.S. have a CV disease, and CV disease is the leading cause of death in the U.S, accounting for one in four deaths.
- A limited number of epidemiologic studies included in the current and previous ISAs have conducted stratified analyses; while they do not clearly demonstrate increased risk across all pre-existing CV diseases. There is some evidence that those with hypertension are at increased risk for $PM_{2.5}$-related health effects compared to those without hypertension, but there are inconsistencies.
- Strong evidence demonstrates that there is a causal relationship between CV effects and short- and long-term exposures to $PM_{2.5}$. Some of the evidence is from studies of panels or cohorts with pre-existing CV disease, which provide supporting evidence but do not directly inform an increase in risk.
- **Overall, the evidence is suggestive that those with pre-existing CV disease, particularly hypertension, may be at increased risk for $PM_{2.5}$ related health effects compared to those without a pre-existing CV disease.**

Cardiovascular disease is the primary cause of death in the U.S., and approximately 12% of adults report a diagnosis of heart disease [Table 12-2; (Blackwell and Villarroel, 2018)]. While evidence demonstrates that a causal relationship exists between short- and long-term $PM_{2.5}$ exposure and cardiovascular effects based on recent evidence, building from studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), evidence addressing whether or not individuals with pre-existing cardiovascular disease are at increased risk for $PM_{2.5}$-associated health effects compared to those without pre-existing CV disease is complex. The evidence examining differential risk for $PM_{2.5}$-related health effects in individuals with pre-existing cardiovascular disease in the 2009 PM ISA (U.S. EPA, 2009) was limited and inconsistent, though studies from the recent literature provide some additional evidence that pre-existing cardiovascular disease may modify the risk of $PM_{2.5}$ for cardiovascular outcomes.

As described in Chapter 6, both previous evidence from the 2009 PM ISA (U.S. EPA, 2009) and recent evidence demonstrate that there is a causal relationship between short- and long-term $PM_{2.5}$ exposure and cardiovascular effects. Both conclusions were informed by evidence for $PM_{2.5}$-related mortality, and hospital admissions and emergency department visits for IHD associated with short-term exposures to $PM_{2.5}$. It is well-recognized that these serious population-level effects are preceded by altered cardiovascular function, though there are no studies that examine differential risk for these serious effects in individuals with and without underlying cardiovascular conditions or diseases. There is, however, evidence from studies examining these serious health effects in only adults with pre-existing cardiovascular disease that demonstrate that $PM_{2.5}$-associated CV effects are observed in this population (Chapter 6). Thus, while this evidence does not inform if those with pre-existing CV disease are at increased risk for a $PM_{2.5}$-related health effect compared to those without pre-existing CV disease, it does indicate that these individuals are at-risk.

Recent studies examining whether there is evidence of increased risk for $PM_{2.5}$-related health effects in people with pre-existing cardiovascular disease have considered an array of specific cardiovascular diseases/conditions (Supplemental Table S12-1) (U.S. EPA, 2018). As was the case for the 2009 PM ISA, hypertension is the most commonly examined cardiovascular disease in epidemiologic studies that conducted stratified analyses. Puett et al. (2009) and Goldberg et al. (2013) both reported positive associations between long-term $PM_{2.5}$ exposure and mortality in the Nurses' Health Study and among older adults in Montreal, Canada, respectively. However, Puett et al. (2009) did not find associations to differ consistently by hypertension status; only associations with fatal CHD, and not mortality or first CHD, were increased for those with hypertension compared to those without. Other studies examining $PM_{2.5}$-related ischemic stroke and incident diabetes also did not find evidence for increased risk among those with hypertension with short-term exposures (Wellenius et al., 2012a; O'Donnell et al., 2011) or long-term exposure (Hansen et al., 2016) (Chen et al., 2013). However, studies examining effect modification for $PM_{2.5}$-associated changes in subclinical CVD outcomes (e.g., blood pressure, inflammation, endothelial dysfunction) provide some evidence that effects in those with hypertension are larger with $PM_{2.5}$ exposure. Both Auchincloss et al. (2008) and Krishnan et al. (2012) conducted analyses within the MESA cohort and observed positive associations for pulse pressure, BAD, and FMD with long-term $PM_{2.5}$ exposure; associations were larger for study participants with hypertension, with the exception of BAD. Wellenius et al. (2013) also found in a study of community-dwelling older adults in Boston that those with hypertension had greater $PM_{2.5}$-related increases in flow velocity and cerebrovascular resistance, measures related to stroke and neurological conditions, with long-term exposure. Interleukin-6 and C-reactive protein, markers of inflammation, were also more strongly associated with long-term exposure to $PM_{2.5}$ in those with hypertension compared to those without (Hajat et al., 2015; Ostro et al., 2014).

Beyond hypertension, recent studies have also evaluated whether there is evidence that people with pre-existing coronary heart disease (CHD) are at increased risk of a PM-related health effect compared to those without CHD. However, all studies are from a single panel of adults from the Heinz Nixdorf Recall study. More specifically, participants in this panel ranged from 45−75 years of age and were from Ruhr area, Germany. Hennig et al. (2014), Viehmann et al. (2015), Hoffmann et al. (2009a), and Fuks et al. (2011) observed positive associations between 12-month $PM_{2.5}$ exposures and CRP, fibrinogen, and BP. When examining effect measure modification by CHD status, only Viehmann et al. (2015) found larger effects in those with CHD compared to those without. Hertel et al. (2010) also examined associations for CRP, and while positive associations across averaging times were observed, effect measure modification by CHD was not clear results varied for 2-day up to 28-day averages of $PM_{2.5}$.

Studies examining effect modification by pre-existing CV diseases other than hypertension or CHD are sparse and vary across outcomes making it difficult to draw conclusions. In addition to the differences across studies in the outcomes and populations examined, results across these studies are inconsistent and do not suggest that individuals with pre-existing CV disease, at a broad level, are at

increased risk for health effects related to short- or long-term exposures to $PM_{2.5}$. However, there is some evidence that those with hypertension, specifically, may be at increased risk compared to those without hypertension.

Evidence from controlled human exposure and animal toxicological studies evaluating whether or no pre-existing CV disease increases risk for $PM_{2.5}$-associated health effects is limited. A single CHE study from the recent literature is available that examined whether use of a respiratory filter could attenuate the cardiovascular effects of acute diesel exhaust (DE) exposure in patients with heart failure (HF) or healthy individuals (Vieira et al., 2016). BP was not significantly changed with DE exposure compared to air controls. When the FILTER-HF patients and healthy controls exercised for 6 minutes, BP increased with exercise in both groups but there were no statistically significant differences with DE exposure with or without filtration and results were similar in those with and without HF. No differences in HRV, HR, endothelial dysfunction, or arterial stiffness were observed for those with or without HF. In addition, the 2009 PM ISA(U.S. EPA, 2009) characterized evidence from studies that evaluated pulmonary outcomes in spontaneously hypertensive rats. These studies found some evidence for pulmonary inflammation following 4-hour to 3-day exposures to CAPs from RTP, NC; various sites in the Netherlands; a high-traffic area in Taiwan, and Detroit (Rohr et al., 2010; Campen et al., 2006; Cassee et al., 2005; Kodavanti et al., 2005; Lei et al., 2004) but lack of a comparison to a normotensive strain limits the utility of these studies in informing differential effects for pre-existing CV disease.

Taken together, the collective evidence is suggestive that individuals with pre-existing CV disease are at increased risk for $PM_{2.5}$-associated health effects compared to those without pre-existing CV disease. The evidence from epidemiologic studies conducting stratified analyses, controlled human exposure, and animal toxicological studies is not clear in describing increased risk across all pre-existing CV disease, but evidence for those with hypertension demonstrates a potential for increased risk. In addition, there is strong evidence described in Chapter 6 supporting a causal relationship between short-term $PM_{2.5}$ exposure and CV effects, based primarily on evidence for ischemic heart disease. As noted, the pathophysiology underlying the serious CV outcomes associated with $PM_{2.5}$ exposure is linked to a variety of underlying CV conditions, though they may be asymptomatic and undiagnosed. This uncertainty in disease diagnoses, and in addition, the variability in disease status complicate the examination of increased risk in these populations.

12.3.2 Pre-existing Diabetes and Metabolic Syndrome

Overview

- Diabetes mellitus is an important component of metabolic syndrome, as well as a risk factor for cardiovascular disease.
- In the 2009 PM ISA, there was limited evidence comparing $PM_{2.5}$-associated health effects in individuals with and without diabetes.
- Recent stratified epidemiologic analyses of short- and long-term $PM_{2.5}$ exposure do not consistently demonstrate increased risk among those with diabetes.
- **Overall, the evidence is inadequate to determine whether individuals with pre-existing diabetes are at increased risk for $PM_{2.5}$-related health effects compared to individuals without diabetes.**

Diabetes mellitus is a group of diseases characterized by high blood glucose levels and affects an estimated 30 million Americans, or 8.8% of the adult population, in 2016 (Blackwell and Villarroel, 2018). In addition, 84 million Americans are estimated to be living with prediabetes, a condition characterized by elevated fasting plasma glucose levels that is also a key risk factor for cardiovascular disease and a component of metabolic syndrome (CDC, 2017). As described in Chapter 7 (Section 7.2.2) metabolic syndrome components (i.e., fasting blood glucose, high blood pressure, dyslipidemia, and obesity) often co-occur and can contribute to atherosclerotic plaque progression causing damage to the vascular system and potentially promoting cardiovascular disease and heart failure. Furthermore, studies have demonstrated cardiovascular and metabolic effects in humans or animal models of diabetes as characterized in Chapter 6 and 7. It is conceivable that biological effects in individuals with diabetes may be further exacerbated by exposures to $PM_{2.5}$. Thus, this section characterizes the evidence informing if individuals with pre-existing metabolic disease, including diabetes, are at increased risk for $PM_{2.5}$-related health effects compared to the individuals without metabolic disease or diabetes.

The 2009 PM ISA (U.S. EPA, 2009) concluded there was some evidence suggesting increased PM-related health effects among those with diabetes; however, much of the evidence was inconsistent across several studies of hospital admission and emergency department visits and short-term PM_{10} exposure, with only one study evaluating the effects of $PM_{2.5}$ (Goldberg et al., 2006). Controlled human exposure and toxicological studies found limited evidence of differences in biomarkers by diabetes status, though the 2009 PM ISA (U.S. EPA, 2009) noted that it was unclear how differences in biomarker responses contribute to overall potential for cardiovascular risk in those with diabetes compared to those without diabetes. Recent epidemiologic and toxicological studies have focused on differential $PM_{2.5}$-related health effects for diabetes status and provide some evidence of increased risk, but there are inconsistencies in results across studies of mortality and cardiovascular outcomes (Supplemental Table S12-2) (U.S. EPA, 2018).

Several studies examined whether diabetes status modified associations between mortality and long-term $PM_{2.5}$ exposure. There was little evidence that $PM_{2.5}$-associated mortality was modified by diabetes status for long- or short-term $PM_{2.5}$ exposure across studies. Several multistate or statewide U.S. based studies of long-term $PM_{2.5}$ exposure reported slight variations in associations, though estimates were generally imprecise (i.e., wide 95% confidence intervals) and changes in risk were small (Wang et al., 2016b; Pope et al., 2014; Puett et al., 2009). One exception was a study of seven southeastern U.S. states, where Wang et al. (2017) observed an increase in risk for mortality associated with long-term $PM_{2.5}$ exposure among Medicare patients who also had a history of diabetes hospital admission compared to those that did not. Furthermore, this modification persisted across simultaneous stratifications of sex and race combinations. Too few studies were available to compare if there were differences by mortality cause. Among studies of short-term $PM_{2.5}$ exposure and mortality, only Goldberg et al. (2013) examined differential risk for $PM_{2.5}$-related mortality by diabetes status. This study demonstrated a slight increase in risk for nonaccidental mortality for cases with diabetes compared to all cases.

A number of studies also examined effect measure modification by diabetes status across an array of cardiovascular outcomes and long-term $PM_{2.5}$ exposure. Studies of incident hypertension and self-reported heart disease found little evidence for differences between individuals with or without diabetes (Hoffmann et al., 2009b; Johnson and Parker, 2009). Chan et al. (2015) and Fuks et al. (2011) observed larger $PM_{2.5}$-related decreases in blood pressure in those with diabetes; however, these differences were modest and imprecise (i.e., wide 95% confidence intervals). In contrast, in a study of the of the Nurses' Health Study cohort by Hart et al. (2015) examining incident CVD among women positive associations were observed for those with diabetes (HR: 1.44, 95% CI: 1.23, 1.68) compared to those without diabetes (HR: 0.94, 95% CI: 0.86, 1.03). Additionally, in a multicity study, Chen et al. (2014) observed a 41% increase in risk of incident hypertension among those with diabetes compared to those without; however, effect estimates were imprecise.

Among evaluations of short-term $PM_{2.5}$ exposure, some studies demonstrated higher risk of cardiovascular effects among individuals with diabetes compared to those without diabetes; while other studies did not observe changes in association based on diabetes status. Across studies, there is limited evidence of differential risk for changes in blood pressure (Wellenius et al., 2012b), heart failure (Haley et al., 2009), or transmural infarctions (Rich et al., 2010). One exception is a multicity study of ischemic stroke hospital admissions as determined by registry data in Ontario, Canada, which reported a positive association among those with diabetes, but observed little evidence of an association among those without diabetes (O'Donnell et al., 2011). Additionally, a panel study in Boston, MA observed little evidence of changes in blood pressure for individuals with well-controlled diabetes compared to a positive change in blood pressure among individuals with poorly controlled diabetes (Hoffmann et al., 2012), which indicates the potential for severity and control of diabetes to be an important factor beyond the presence or absence of the disease.

Several recent epidemiologic studies evaluated cardiovascular effects and measures of inflammation related to atherosclerosis in individuals exposed to PM and found larger, though imprecise, associations in participants with diabetes compared to those without. In a study of the MESA cohort, Allen et al. (2009) observed positive associations between $PM_{2.5}$ levels (2 year average) and elevated risk for calcification among individuals with diabetes. Furthermore, in those diabetic individuals with some or no calcification there was a positive change in the Agatston Score (a metric for coronary artery calcification). In other studies of the MESA cohort, Roux et al. (2008) observed no differences in associations between 20 year $PM_{2.5}$ averages and health measures of atherosclerosis by diabetes status. Additionally, Roux et al. (2008) and Van Hee et al. (2011) did not observe effect measure modification for $PM_{2.5}$-associated changes in QT-prolongation or ventricular conduction delay by diabetes status. In a German population-based cohort study (Heinz Nixdorf Recall study), Bauer et al. (2010) found a slightly weaker association between $PM_{2.5}$ exposure and carotid intima-media thickness (CIMT) for those with diabetes compared to those without.

Other studies specifically evaluated effect measure modification of associations between long- and short-term $PM_{2.5}$ exposure and markers of inflammation and coagulation (e.g., IL-6, CRP, and fibrinogen) by diabetes status. Specifically, in a study of 6 U.S. cities, Ostro et al. (2014) found the association between CRP and long-term $PM_{2.5}$ exposure to be modified by diabetes, with particularly large increases in CRP when comparing diabetes status among older adults. In contrast, Hoffmann et al. (2009a) conducted stratified analyses of the German Heinz Nixdorf Recall Study and found no distinct effect by diabetes status on PM associations with fibrinogen or CRP. In a study of short-term $PM_{2.5}$ exposure using the same German population-based cohort, Hertel et al. (2010) observed no distinct effect by diabetes status on the PM association with CRP.

Overall, evidence is inadequate to determine whether individuals with pre-existing diabetes are at increased risk for $PM_{2.5}$-associated health effects compared to those without diabetes. A number of recent studies provide inconsistent evidence for increased risk across a range of health effects associated with exposure to $PM_{2.5}$. Epidemiologic studies of diabetes predominantly evaluated associations between mortality and cardiovascular outcomes and long-term $PM_{2.5}$ exposure. Several studies reported elevated risk among those with diabetes; however, results were inconsistent within and across health outcomes. One important limitation for many studies was the small proportion of participants with diabetes, contributing to imprecise effect estimates (i.e., wide 95% confidence intervals). Additionally, as observed by Hoffmann et al. (2012), there may differences in response to PM exposure between those with well-controlled versus poorly controlled diabetes; however, few studies include this level of detail. Interpretation of the evidence is further complicated by the lack of information on individuals with prediabetes, which may exhibit similar underlying metabolic characteristics as those with diabetes. Relying solely on a clinical diagnosis may underestimate the population at increased risk and potentially introduce bias by similarly grouping those in a healthy metabolic state with those in a prediabetic metabolic state.

12.3.3 Obesity

Overview

- Obesity affects nearly a third of adults in the U.S. and is associated with low-grade inflammation that potentially interact with PM-related inflammation.
- Evidence indicates the potential for dosimetric differences for $PM_{2.5}$ among adults and children by obesity status.
- Evidence from recent stratified epidemiologic analyses of long-term $PM_{2.5}$ exposure and mortality suggest increased risk for those who are obese compared to those who are not; evidence for other outcomes is inconsistent.
- Variability in the definition of obesity limits comparability between studies and the ability to distinguish risk between those who are overweight and obese.
- **Overall, the evidence is suggestive of increased risk for $PM_{2.5}$-related health effects among those who are obese compared to those who are not.**

In the U.S., obesity is defined as a BMI of 30 kg/m^2 or greater, with a BMI between 25 and 30 kg/m^2 indicating an overweight individual. It is a public health issue of growing importance as obesity rates in adults have continually increased over several decades in the U.S., reaching an estimated 30% in 2016 (Blackwell and Villarroel, 2018). Furthermore, 36% of adults in the U.S. are considered overweight while 34% are at a healthy weight (BMI 18.5−25 kg/m^2) (Blackwell and Villarroel, 2018). Obesity or high BMI could potentially increase the risk of PM related health effects through multiple mechanisms. For example, persistent low grade inflammation associated with obesity or excess nutrients and energy (CN and AR, 2011; Gregor and Hotamisligil, 2011; Lumeng and Saltiel, 2011) may work in conjunction with PM related inflammation that is thought to facilitate atherosclerotic plaque progression (Section 6.3.1, Figure 6-11). Obesity is closely related to diabetes, and is one component of metabolic syndrome, where co-occurring factors may also be associated with PM exposure (Section 7.2.1, Figure 7-2) and further facilitate cardiovascular risk (Section 6.3.1). Nutritional access and poor diet (Section 12.6.2) may also be potential risk factors that act in combination with obesity. Additionally, those who are obese may experience greater particle deposition in the lung as there is evidence of increased ventilation rates for overweight or obese adults and children, as well as a lower nasal breathing fraction and increase deposition fraction among obese children (Section 4.1.3, Section 4.2.4.4).

The 2009 PM ISA evaluated several studies that reported differences in subclinical cardiovascular and inflammatory markers between obese and nonobese participants in association with short-term exposure to $PM_{2.5}$(Dubowsky et al., 2006; Schwartz et al., 2005; Bennett and Zeman, 2004). A number of recent studies examining effect measure modification $PM_{2.5}$-related health effects by obesity statues are available and have reported some evidence of increased risk for mortality among obese individuals; however, evidence in studies across the range of effects examined including cardiovascular disease, incident diabetes, reproductive, and development outcomes do not consistently indicate differential risk by obesity status (Supplemental Table S12-3) (U.S. EPA, 2018).

Several studies examined effect measure modification of associations between mortality and long-term $PM_{2.5}$ exposure by obesity status. Overall, there was a trend across studies of increased risk among those who were overweight or obese compared to those of normal weight, though there are some exceptions to this trend across studies, and effect estimates are imprecise (i.e., wide 95% confidence intervals). A number of multicity studies in the U.S., Canada, and Europe reported increased risk for mortality among those who were obese (Villeneuve et al., 2015; Beelen et al., 2014a; Beelen et al., 2014b; Weichenthal et al., 2014; Puett et al., 2009). However, Turner et al. (2011) reported decreasing risk as BMI increased, including a 14% decrease in risk for those overweight compared to normal BMIs and a negative association among obese individuals. Furthermore, it is possible there is some variation by underlying cause of mortality. For example, Pinault et al. (2016) observed marginal decreases in risk for all-cause and cardiovascular mortality among those who were obese, though they reported a 35% increase in risk for respiratory mortality among obese participants. In contrast to these results, a pooled analysis of European cohorts observed that as BMI increased the association between $PM_{2.5}$ and respiratory mortality declined, while the opposite was true for all-cause and cardiovascular mortality (Beelen et al., 2014a; Beelen et al., 2014b; Dimakopoulou et al., 2014).

Studies have also examined a differential risk for a variety of cardiovascular effects by obesity status. In general, studies found little evidence for differences between obese and nonobese individuals, and when changes in association were present, they tended to be modest and imprecise. For example, a registry study of long-term $PM_{2.5}$ exposure and incident hypertension in Ontario, Canada (Chen et al., 2014) reported a decrease in risk for obese participants (HR: 1.07, 95% CI: 0.91, 1.26) compared to nonobese participants (HR: 1.17, 95% CI: 1.04, 1.33). Likewise, an examination of the Nurses' Health Study reported an increased risk in incident cardiovascular disease for obese participants (HR: 1.12, 95% CI: 0.99, 1.30) compared to nonobese participants (HR: 0.99, 95% CI: 0.88, 1.12) (Hart et al., 2015). A number of studies also examined changes in blood pressure with both long-term (Chan et al., 2015; Fuks et al., 2011) and short-term (Hoffmann et al., 2012; Wellenius et al., 2012b) exposures to $PM_{2.5}$ and observed no consistent pattern by obesity status for changes in blood pressure. Other studies examined outcomes such as prevalence of heart disease (Johnson and Parker, 2009) or measures of atherosclerosis (Hoffmann et al., 2009b) and did not observe an increase in risk among those who were obese compared to those with healthy weight.

Several of the studies that examined cardiovascular endpoints related to atherosclerosis and modification by diabetes status, as previously described (Section 12.3.2), also examined potential modification by obesity and observed limited evidence of increased risk among obese participants compared to those or healthy weight. In a study of the MESA cohort, Allen et al. (2009) identified positive $PM_{2.5}$ associations with elevated risk for calcification among obese individuals compared to those of normal weight. Furthermore, in those obese individuals with some or no calcification a positive change in the Agatston score (measure of coronary artery calcification) was observed. A similar study of the MESA cohort estimated the effect of 20 year $PM_{2.5}$ averages on atherosclerosis health measures and found no differences in association by BMI category (Roux et al., 2008). In a German population-based

cohort study (Heinz Nixdorf Recall study) Bauer et al. (2010) found a slightly stronger association between $PM_{2.5}$ exposure and carotid intima-media thickness (CIMT) for obese participants compared to those of normal weight.

Other studies specifically evaluated effect modification by obesity status on associations between markers of inflammation and coagulation, including IL-6, CRP, and fibrinogen. Hoffmann et al. (2009a) and Hertel et al. (2010) conducted analyses from German Heinz Nixdorf Recall Study cohort and found no distinct effect by obesity status on $PM_{2.5}$ associations with fibrinogen or CRP. A Study of Women's Health Across the Nation (SWAN), demonstrated increased CRP for middle aged obese women, though estimates had wide confidence intervals (Ostro et al., 2014).

A limited number of studies investigated effect measure modification by obesity for associations between $PM_{2.5}$ and other health endpoints, such as incident diabetes and reproductive outcomes. Among studies of incident diabetes, results were inconsistent. A study in Ontario, Canada reported decreased risk of developing diabetes among the overweight and obese (Chen et al., 2013), while multicity studies in Denmark (Hansen et al., 2016) and Germany (Weinmayr et al., 2015) reported increased risk among the obese compared to healthy weight. Among studies of reproductive outcomes, insufficient studies were available to report any trends for a specific outcome; however, there was little evidence of modification by obesity status in studies of endometriosis (Mahalingaiah et al., 2014), and gestational diabetes (Robledo et al., 2015). Conversely, in a small study of preeclampsia among predominantly Hispanic women in Los Angeles, Mobasher et al. (2013) reported higher risks among nonobese women based on $PM_{2.5}$ exposures in the first trimester compared to obese women.

Overall, the available evidence is suggestive of increased risk among those who are obese compared to those who are not obese for $PM_{2.5}$-associated health effects. There is a relatively consistent evidence across a small evidence base demonstrating increased risk of $PM_{2.5}$-associated mortality among those who are obese or overweight compared to those of healthy weight. Results from other outcomes were less consistent, although some studies observed increased risk in markers of atherosclerosis as well as incident diabetes. An important limitation across studies was the variability in categorizing obesity, with thresholds defining obesity ranging from a BMI of 27 to 30.6 kg/m^2. Furthermore, many studies did not distinguish between being overweight or obese and included overweight individuals either with obese individuals or with healthy weight individuals.

12.3.4 Elevated Cholesterol

Overview

- Elevated cholesterol is a common chronic condition in the U.S. adult population and is an important risk factor for other serious health conditions associated with $PM_{2.5}$ exposure, such as cardiovascular disease and diabetes.
- The 2009 PM ISA did not evaluate cholesterol status, but some recent studies have examined differences $PM_{2.5}$-associated health effects in the context of lipid disorders. This limited epidemiologic evidence provides evidence of increased risk with short- and long-term $PM_{2.5}$ exposure for those with elevated cholesterol compared to normal cholesterol.
- Additional epidemiologic studies stratifying by cholesterol medication (i.e., statins) usage provide limited evidence of increased risk of cardiovascular disease among statin users compared to those not taking statins.
- **Overall, the evidence is inadequate to determine if adults with elevated cholesterol are at increased risk for $PM_{2.5}$-related health effects.**

Elevated blood cholesterol is a common chronic health condition in the U.S., with the prevalence of hypercholesterolemia in the U.S. adult population approximately 26.0%, as reported by the 1999−2006 National Health and Nutrition Examination Surveys (Fryar et al., 2010). Metabolic disruption, such as dyslipidemia, can increase the risk of other health conditions, such as cardiovascular disease and diabetes. Additionally, as examined in Chapter 6 and Chapter 7, there is some evidence that short-term (Section 6.3.5, Section 7.1.3.3) and long-term (Section 6.3.12, Section 7.2.5.5) $PM_{2.5}$ exposures are associated with changes in blood lipids. While elevated blood cholesterol is an important health risk factor, few studies have explicitly investigated if blood cholesterol status increases the risk of other health outcomes associated with $PM_{2.5}$ exposure.

The PM 2009 ISA (U.S. EPA, 2009) did not evaluate studies examining potential differences in populations based on cholesterol. A limited number of epidemiologic studies have investigated differences between populations with and without high cholesterol, or by statin usage, and observed some evidence of higher risk for $PM_{2.5}$ related mortality and cardiovascular outcomes (Supplemental Table S12-4) (U.S. EPA, 2018). While these studies indicate those with elevated cholesterol, or those who use statins, may have potentially higher risks, overall, there were insufficient studies available to determine if cholesterol status consistently modifies health outcomes associated with $PM_{2.5}$ exposure.

In a study of 13 northeastern U.S. states, using data from the NHS cohort, Puett et al. (2009) evaluated the potential for effect measure modification by hypercholesterolemia status with $PM_{2.5}$ exposure over the 12-months prior to all-cause mortality, or a fatal coronary heart disease (CHD) event. In stratified analyses, the authors observed increased risk among those with hypercholesterolemia (HR: 1.53, 95% CI: 1.15−2.03) compared to those without hypercholesterolemia (HR: 1.04, 95% CI: 0.77−1.40). Puett et al. (2009) observed a similar trend among a smaller subset of fatal CHD cases. A

small study of myocardial infarction hospital admissions in Rochester, NY also observed a larger positive association among patients with history of dyslipidemia (Gardner et al., 2014).

In addition to studies with information on direct measures of blood cholesterol or patient history of dyslipidemia, several studies stratified study populations by use of statins or lipid-lowering medication. Long-term exposure studies in the U.S. and Germany (Bauer et al., 2010; Allen et al., 2009), as well as a meta-analysis of randomized controlled trials in Los Angeles (Künzli et al., 2010) observed increased risk of atherosclerosis associated with $PM_{2.5}$ exposure among those using statins compared to those not using statins. Studies of other health measures and long-term $PM_{2.5}$ exposure, such as history of peripheral vascular disease (Hoffmann et al., 2009b), and platelet counts (Viehmann et al., 2015) also observed increased risk among individuals using statins. A U.S. based study, using data from the MESA cohort, did not observe any substantial changes in $PM_{2.5}$-related flow-mediated dilation; however, they observed a positive association in baseline arterial diameter among those using statins compared to no change for those not using statins (Krishnan et al., 2012). Conversely, studies of short- and long-term exposure that investigated systemic inflammation found decreased responses for biomarkers of systemic inflammation among those using statins (Viehmann et al., 2015; Ostro et al., 2014; Hertel et al., 2010); however, many statins have anti-inflammatory properties complicating interpretation of these results.

Overall, the limited evidence is inadequate to determine if elevated cholesterol increases risk for $PM_{2.5}$-related health effects compared to cholesterol in the normal range. A single long-term exposure study reported elevated risk among those with hypercholesterolemia for $PM_{2.5}$-related mortality, while a single short-term study reported elevated risk of ST-Elevation Myocardial Infarction. Several studies examining biomarkers or preclinical measures of atherosclerosis and vascular function provide some evidence of elevated cardiovascular disease risk among statin users; however, the evidence base is small. Other studies examined if statin usage modified $PM_{2.5}$-related systemic inflammation; however, many statins have known anti-inflammatory properties, making these studies less informative in determining whether those with elevated cholesterol exhibited differential subclinical responses due to $PM_{2.5}$ exposure. Further limitations among studies of statins include the relatively low proportion of participants who used statins, leading to less precise estimates (i.e., wide 95% confidence intervals), as well as the difficulty in interpreting how representative statin prescription information is for control of blood lipid disorders among populations using statins.

12.3.5 Pre-existing Respiratory Disease

Overview

- The most common chronic respiratory diseases in the U.S. are asthma and COPD. Asthma affects a substantial fraction of the U.S. population, and it is the leading chronic disease among children. COPD primarily affects older adults and contributes to compromised respiratory function and underlying pulmonary inflammation.
- There is strong evidence indicating $PM_{2.5}$-associated respiratory effects among those with asthma, which forms the primary evidence base for the likely to be causal relationship between short-term exposures to $PM_{2.5}$ and respiratory health effects (Chapter 5).
- Few studies are available from the recent literature or in the 2009 PM ISA that inform whether those with asthma are at disproportionate risk for $PM_{2.5}$-related health effects compared to those without asthma.
- While there is some evidence of $PM_{2.5}$-related health effects in individuals with COPD, there are few studies from the current and previous ISAs with stratified analyses to compare effects in individuals with and without COPD
- **Overall, there is suggestive evidence that individuals with respiratory disease, particularly asthma, may be at increased risk for $PM_{2.5}$-related health effects compared to those without respiratory disease.**

Asthma

Approximately 8.3% of adults and 8.4% of children (age <18 years) in the U.S. currently have asthma (Blackwell and Villarroel, 2018), and it is the leading chronic illness affecting children. With regard to consideration of those with asthma potentially being at increased risk for a $PM_{2.5}$-related health effect, it is important to note that individuals with asthma, and children, tend to have a higher degree of oronasal breathing, which can result in greater penetration of PM into the lower respiratory tract (Section 4.1.3). Furthermore, there is limited evidence demonstrating that individuals with asthma may have altered clearance of particles (Section 4.3.4).

The 2009 PM ISA concluded that individuals with asthma may be more susceptible to health effects related to PM based on a limited number of epidemiologic studies for respiratory effects and controlled human exposure and animal toxicological studies demonstrating biological plausibility for asthma exacerbation with exposures to $PM_{2.5}$. Consistent with this, recent evidence evaluated in this ISA supports that there is likely to be a causal relationship between short-term exposure to $PM_{2.5}$ and respiratory effects, based primarily on evidence for asthma exacerbation in epidemiologic studies (Section 5.1.2) with supporting evidence across disciplines that provides biological plausibility (Section 5.1.1). Given this evidence, it is clear that individuals with asthma experience $PM_{2.5}$-related respiratory effects; however, evidence informing an increase in risk compared to those without asthma is limited.

There continue to be few studies that provide comparisons between individuals with and without asthma (Supplemental Table S12-5) (U.S. EPA, 2018). The 2009 PM ISA (U.S. EPA, 2009) included only a handful of epidemiologic and controlled human exposure studies examining $PM_{2.5}$ or CAPs exposures that provided some evidence for increased risk. Recent evidence is also limited to a few epidemiologic studies with stratified analyses for asthma for a variety of disparate outcomes. Of these studies, Watanabe et al. (2015) and Prieto-Parra et al. (2017) are most informative as they examined respiratory outcomes (i.e., lung function and symptoms) in children with and without asthma. Both studies demonstrated positive associations with short-term exposures to $PM_{2.5}$ for those without asthma, but symptoms and lung function decrements were of greater magnitude in children with asthma.

Other studies examined nonrespiratory outcomes. A study measuring cytokine responsiveness in blood samples collected from children with and without asthma in Germany demonstrated $PM_{2.5}$-related proinflammatory responses in children with asthma that were not observed in children without asthma for short-term exposures. In a multicity U.S. study in adults, $PM_{2.5}$ associated lung cancer mortality was greater in those with asthma compared to those without provide some evidence for increased risk in those with asthma compared to those without (Klümper et al., 2015; Turner et al., 2011). Bunch et al. (2011) conducted a study in Utah of hospital admissions with a primary diagnosis of atrial fibrillation and observed generally positive associations with $PM_{2.5}$ in those with and without asthma. In a study of diabetes incidence in Ontario, Canada, Chen et al. (2013) observed individuals with asthma to be at slightly decreased risk for diabetes with long-term exposures to $PM_{2.5}$ compared to those without.

Chronic Obstructive Pulmonary Disease (COPD)

Chronic lower respiratory disease, including COPD, was ranked as the third leading cause of death in the U.S. in 2011 (Hoyert and Xu, 2012). COPD comprises chronic bronchitis and emphysema and affects approximately 6.8 million adults in the U.S., respectively (Table 12-2). Given that people with COPD have compromised respiratory function and underlying systemic inflammation, it is plausible that they could be at increased risk for an array of $PM_{2.5}$-related health effects. Furthermore, there was some evidence to suggest differences in dosimetry, including greater deposition and impaired mucociliary clearance, that is also described in this ISA (Sections 4.2.4.7 and 4.3.4).

The 2009 PM ISA (U.S. EPA, 2009) described inconsistent results across a small evidence base examining differential $PM_{2.5}$-related respiratory effects in individuals with COPD and those without. In the current review, there continues to be limited evidence examining differential risk by COPD status and most of the available studies have focused on cardiovascular outcomes (Supplemental Table S12-5) (U.S. EPA, 2018). Wang et al. (2017) and Turner et al. (2011) observed greater risk for mortality associated with long-term exposures to $PM_{2.5}$ for those with COPD in a multicity study in the U.S. However, studies for cardiovascular hospitalizations (i.e., atrial fibrillation, myocardial infarction, acute coronary syndrome, and heart failure), incident hypertension, and diabetes incidence did not consistently demonstrate that those with COPD are at greater risk than those without in studies of short- and long-term